

DOPAMINE TRANSPORTER IMAGING AGENTS

FIELD OF THE INVENTION

The present invention relates to coordination complexes comprising a radiolabeled ligand with high binding affinity and good selectivity for the dopamine transporter (DAT). Such agents can be useful for the early diagnosis and treatment of neurodegenerative disorders.

BACKGROUND OF THE INVENTION

The dopamine transporter (DAT) plays a critical role in physiological, pharmacological and pathological processes in brain. The transport system is a primary mechanism for terminating the effects of synaptic dopamine, thereby contributing to the maintenance of homeostasis in dopamine systems. It also appears to be a principal target of cocaine in the brain. (Kennedy and Hanbauer, *J. Neurochem.* 1983, 41, 172-178; Shoemaker et al., *Naunyn-Schmeideberg's Arch. Pharmacol.* 1985, 329, 227-235; Reith et al., *Biochem Pharmacol.* 1986, 35, 1123-1129; Ritz et al., *Science* 1987, 237, 1219-1223; Madras et al., *J. Pharmacol. Exp. Ther.* 1989a, 251, 131-141; Bergman et al., *J. Pharmacol. Exp. Ther.* 1989, 251, 150-155; Madras and Kaufman, *Synapse* 1994, 18, 261-275). Furthermore, the dopamine transporter may be a conduit for entry of neurotoxins into dopamine containing cells.

The striatum has the highest levels of dopamine terminals in the brain. A high density of DAT is localized on dopamine neurons in the striatum and appears to be a

marker for a number of physiological and pathological states. For example, in Parkinson's disease, dopamine is severely reduced and the depletion of DAT in the striatum has been an indicator for Parkinson's disease (Schoemaker et al., *Naunyn-Schmeideberg's Arch. Pharmacol.* 1985, 329, 227-235; Kaufman and Madras, *Synapse* 1991, 9, 43-49). Consequently, early or presymptomatic diagnosis of Parkinson's disease can be achieved by the quantitative measurement of DAT depletion in the striatum. (Kaufman and Madras, *Synapse* 1991, 9, 43-49). Simple and noninvasive methods of monitoring the DAT are quite important. Depletion could be measured by a noninvasive means such as brain imaging using a scintillation camera system and a suitable imaging agent (Frost et al., *Ann. Neurology* 1993, 34, 423-431; Hantraye et al., *Neuroreport* 1992, 3, 265-268). Imaging of the dopamine transporter also would enable the monitoring of progression of the disease and of reversal of the disease such as with therapies consisting of implants of dopamine neurons or drugs that retard progression of the disease.

Other neuropsychiatric disorders, including Tourette's Syndrome and Lesch Nyhan Syndrome and possibly Rett's syndrome, are also marked by changes in DAT density. The DAT also is the target of the most widely used drug for attention deficit disorder, methylphenidate. The capacity to monitor the transporter in persons suffering from this disorder can have diagnostic and therapeutic implications. Furthermore, an age-related decline in dopamine neurons can be reflected by a decline in the dopamine transporter (Kaufman and Madras, *Brain Res.* 1993, 611, 322-328; van Dyck et al., *J. Nucl. Med.* 1995, 36, 1175-1181) and may provide a view on dopamine deficits that lie outside the realm of neuropsychiatric diseases.

The density of the DAT in the brains of substance abusers has also been shown to deviate from that in normal brain. For example, the density is elevated in post-mortem tissues of cocaine abusers (Little et al., *Brain Res.* 1993, 628, 17-25). On the other hand, the density of the DAT in chronic nonviolent alcohol abusers is decreased markedly. (Tiihonen et al., *Nature Medicine* 1995, 1, 654-657). Brain imaging of substance abusers can be useful for understanding the pathological processes of cocaine and alcohol abuse and monitoring restoration of normal brain function during treatment.

Accordingly, a radiopharmaceutical that binds to the DAT can provide important clinical information to assist in the diagnosis and treatment of these various disease states.

In order to be effective as an imaging agent for the disorders described above, it must have a specific binding affinity and selectivity for the transporter being targeted, e.g. DAT. Brain imaging agents must also have blood brain barrier (BBB) permeability. Yet, it has been difficult to produce a metal chelate which can cross the blood brain barrier while still retaining binding affinity and selectivity for its receptor site. Therefore, it is very desirable to find a suitable agent that satisfies these criteria and will complex with a desired radionuclide, such as ^{99m}Tc .

In addition, to be an effective imaging agent, a specific target:nontarget ratio is necessary. In the case of an agent selective for DAT one must take into account the

fact that the striatum, the region of the brain having the highest density of the dopamine transporter, also contains serotonin transporter (SET). The SET is normally present at one-tenth to one-fifteenth the concentration of the dopamine transporter. Imaging agents that bind very strongly to DAT sometimes also exhibit a degree of binding to SET. Although such a nontarget binding typically poses no serious problem in the imaging of normal brains due to the greater number of DAT compared to SET, under disease conditions in which DAT are selectively reduced (or in which SET may be selectively increased), binding to the SET may make it difficult to quantify DAT. Moreover, binding to SET in other brain regions such as the hypothalamus and thalamus can reduce striatal contrast and diminish accuracy in localizing and imaging the striatum. Therefore, the target to nontarget binding ratio of DAT:SET can be important. Presently, among the most effective compounds for viewing and quantifying the DAT are phenyltropane derivatives that are labelled with positron emitters, such as ^{11}C and ^{18}F , and gamma emitters, such as ^{123}I .

The radionuclide, technetium-99m, $^{99\text{m}}\text{Tc}$ ($T_{1/2}$ 6.9h, 140KeV gamma ray photon emission) is a preferred radionuclide for use in imaging because of its excellent physical decay properties and its chemistry. For example, its half-life of about 6 hours provides an excellent compromise between rate of decay and convenient time frame for an imaging study. Thus, it is much preferred to other radionuclides such as ^{123}I , which has a substantially longer half life, or ^{18}F , which has a substantially shorter half-life, and which are much more difficult to use. Its emission characteristics also make it easy to image. Further, it can be conveniently generated at the site of use. $^{99\text{m}}\text{Tc}$ is currently the radionuclide of choice in diagnostic centers

around the world. It would be desirable to have a coordination complex with technetium for imaging DAT. Such a complex could be used for detecting conditions in which the DAT is useful as a marker.

5 However, a number of difficulties arise in the use of technetium for radioimaging agents because of its chemistry. For example, ^{99m}Tc must typically be bound by a chelating agent. Consequently it is much more difficult to design and prepare a ^{99m}Tc radioligand than it is to prepare a radioligand using other radionuclides such as ^{123}I , which can be attached covalently to the ligand. The size of
10 the chelating agent for technetium also can create problems when using this radionuclide in imaging agents. This can be an especially difficult problem when attempting to design receptor-based imaging agents using Tc.

 Imaging agents being tested to determine their ability as diagnostic tools for
15 neurodegenerative diseases typically are ^{123}I labeled radioiodinated molecules. See, for example, RTI-55 (Boja, J.W., et al., *Eur. J. Pharmacol.* 1991, 194, 133-134; Kaufman and Madras, *Synapse*, 1992, 12, 99-111) or β -CIT (Neumeyer, J.L., et al., *Med. Chem.* 1991, 34, 3144-3146) and an iodoallyltropane, altropane (Elmaleh, D.R., et al., *US Patent No. 5,493,026*.

20 Although the tropane family of compounds are known to bind to the dopamine transporter, the addition of bulky chelating ligands for binding technetium or rhenium would be expected to affect potency and ability to cross the blood brain barrier of the resulting labeled complex. Kung, et al., in *Technetium and Rhenium in*

Chemistry and Nuclear Medicine 4, eds. M. Nicolini, G. Bandoli, U. Mazzi, Servizi Grafici Editoriali, Padua, 1995, report that a ^{99}Tc -labelled N_2S_2 ligand complexed with an arylpiperazine known to have selective binding to serotonin $_{1A}$ had only moderate binding affinity *in vitro* and failed to penetrate the intact blood-brain barrier.

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It would be desirable to have a technetium or rhenium radio-labelled DAT imaging agent which is capable of crossing the blood brain barrier and has a high binding affinity and selectivity for the DAT.

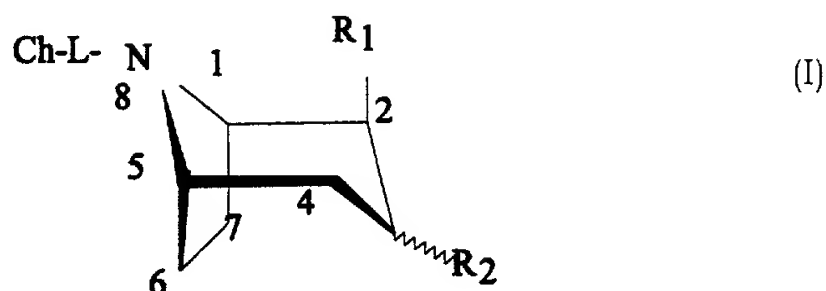
10 SUMMARY OF THE INVENTION

The present invention provides radiopharmaceutical compounds that form coordination complexes with a technetium or rhenium radionuclide and that selectively bind to dopamine transporters, thereby providing novel radio labeled agents. Preferred such agents include radioimaging agents which are capable of
15 crossing the blood brain barrier to image DAT in the brain.

The compounds of the present invention comprise a tropane compound linked through the N atom at the 8-position to a chelating ligand capable of complexing a technetium or rhenium radionuclide to produce a neutral labeled complex that
20 selectively binds to the dopamine transporter. These compounds can be prepared as separate diastereoisomers as well as a mixture of diastereoisomers.

Tropane compounds useful in the practice of the present invention bind to the dopamine transporter. Preferred radiopharmaceutical compounds of the invention

can be represented by the following structural formula:



wherein R_1 is α or β and is selected from COOR^a , COR^a , and $\text{CON}(\text{CH}_3)\text{OR}^a$;

R_2 is α or β and is selected from $\text{C}_6\text{H}_4\text{X}$, $\text{C}_6\text{H}_3\text{XY}$, $\text{C}_{10}\text{H}_7\text{X}$, and $\text{C}_{10}\text{H}_6\text{XY}$;

R^a is selected from $\text{C}_1 - \text{C}_5$ alkyl, e.g. methyl, ethyl, propyl, isopropyl, etc.;

X and Y are independently selected from R^a , H, Br, Cl, I, F, OH, and OCH_3 ;

L is $-(\text{CH}_2)_n$ where n is an integer from 1 to 6, or $-(\text{CH}_2)_n - (\text{aryl, arylalkyl, ethenyl or ethynyl}) - (\text{CH}_2)_m$ where the sum of n plus m is an integer from 1 to 6; and

Ch is a tridentate or tetradentate chelating ligand that forms a neutral complex with technetium or rhenium,

and further wherein the bond between C_2 and C_3 is either a single bond or a double bond.

Thus, R_1 and R_2 can be in the α or β configuration. Further, R_1 preferably can be substituted at the C_2 or C_4 when the tropane has a 1R or 1S configuration,

respectively. The chelating ligand, if chiral, can be *syn* or *anti* with R, S, or RS.

The imaging agents of the present invention are useful for detecting tropane recognition sites including neuronal transporters such as the dopamine transporter.

5 For purposes of the present invention, a tropane recognition site is any receptor or transporter site that binds to the tropane compound. Thus, the compounds of this invention can be used as diagnostic agents, prognostic agents and therapeutic agents for neurodegenerative diseases.

10 The present invention also provides a method of using the coordination complex as an imaging agent for detecting neurodegenerative and neuropsychiatric disorders characterized by a change in density of DAT or dopamine neurons. For example, a method for detecting the change in DAT resulting from a neurodegenerative disease, such as Parkinson's disease, comprises injecting a labeled
15 compound of the present invention in a dose effective amount for detecting DAT in the particular mammal and obtaining images of the labeled compound bound to DAT. Rhenium labeled compounds can also be useful for therapeutic treatments.

The present invention also provides kits for producing the compounds of the
20 present invention labeled with technetium or rhenium. The kits typically comprise a sterile, non-pyrogenic container containing lyophilized compound and a reducing agent to form a complex of the compound with technetium or rhenium. The kits permit ready reconstitution and labeling with aqueous solutions containing the radionuclide, e.g. pertechnetate, preferably having a pH in the range of about 5 to

about 8.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an illustration of alternative general reaction schemes for linking a
5 N_2S_2 chelating ligand to a nortropane analog and labeling with a metal "M", which can
be technetium or rhenium.

FIG. 2 is an illustration of a general scheme for preparation of 2-carbomethoxy
tropanes (Scheme 1) comprising an aryl octene in accord with the present invention
10 and subsequent preparation of 3α and 3β diastereomers thereof.

FIGs. 3 and 4 are illustrations of a general scheme for preparation of 2-
ethylketo analogs (Schemes 2 and 3) of radiopharmaceutical compounds in accord
with a preferred embodiment of the present invention.

FIG. 5 is an illustration of a general scheme for preparation of 2-carboxamido
3 α - or 3 β - aryl analogs (Scheme 4) of radiopharmaceutical compounds in accord with
15 a preferred embodiment of the present invention.

FIG. 6 is an illustration of a general reaction scheme for preparation of 3-aryl-
20 2-ethylketo-2,3-ene analogs (Scheme 5) of radiopharmaceutical compounds in accord
with a preferred embodiment of the present invention.

FIG. 7 is an illustration of a general reaction scheme for preparation of 3-aryl-

2-carbomethoxy-2,3-ene analogs (Scheme 6) of radiopharmaceutical compounds in accord with a preferred embodiment of the present invention.

FIG. 8 is an illustration of a general scheme for converting the 3α and 3β diastereomers of FIG. 2 to bistrityl protected N_2S_2 tropanes and labeling with technetium or rhenium (Scheme 7).

FIG. 9 is an illustration of an alternative general reaction scheme for preparation of 3-aryl-2-ethylketo-2,3-ene analogs (Scheme 8) of radiopharmaceutical compounds in accord with a preferred embodiment of the present invention.

FIG. 10 is an illustration of a general reaction scheme for preparation of 3-naphthyl-2-carbomethoxy-2,3-ene and 3α -naphthyl or 3β -naphthyl analogs (Scheme 9) of radiopharmaceutical compounds in accord with a preferred embodiment of the present invention.

FIG. 11 is a HPLC chromatogram of ^{99m}Tc labeled O-1505T.

FIG. 12 is a HPLC chromatogram of ^{99m}Tc labeled O-1508T.

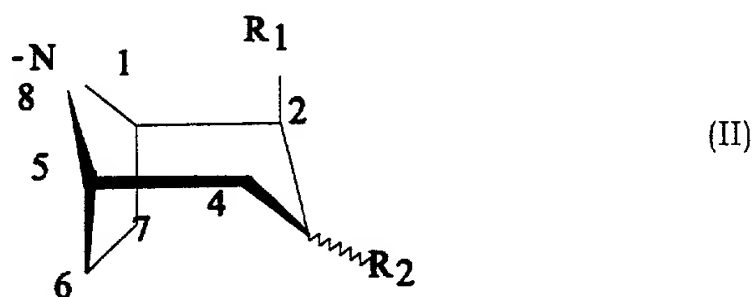
FIG. 13 is a HPLC chromatogram of ^{99m}Tc labeled O-1561T.

FIG. 14 is a HPLC chromatogram of ^{99m}Tc labeled O-1560T.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention comprise a tropane compound or ligand that selectively binds to tropane recognition sites, e.g., neuron transporters such as the DAT. The tropane ligand is radiolabeled with a radioactive technetium or rhenium by a chelating ligand which is attached to the tropane ligand by a linker. The unlabeled compounds of this invention are schematically represented by the formula Ch-L-Tr, wherein Ch is the chelating ligand, L is the linker and Tr is the tropane ligand.

Tropane compounds or ligands useful in the practice of the present invention can generally be represented by formula II where R_1 and R_2 are defined as above and where R_1 can also be substituted at the C_4 position of the tropane ring:

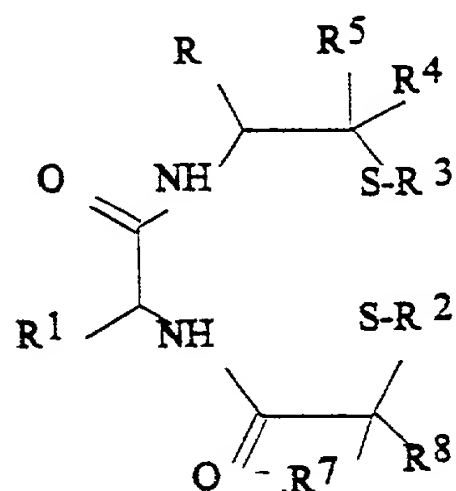


Any tropane compound of the general formula II is useful in the present invention so long as it binds to DAT. Examples of particularly useful tropanes are: 2-carbomethoxy-3-(4-fluorophenyl)-N-methyltropane ("WIN 35,428") (Clarke, R.L., et al., *J. Med. Chem.* 1973, 16, 1260-1267) which binds potently ($IC_{50}=11.0$ nM) and with specificity to the DAT (Meltzer, P.C., et al., *J. Med. Chem.* 1993, 36, 855-862); 2-carbomethoxy-3-(3,4-dichlorophenyl)-N-methyltropane ("O-401"; $IC_{50}=1.09$ nM) (Meltzer, P.C., et al., *J. Med. Chem.* 1993, 36, 855-862). Tropane analogs that have a

3 α - group are of the boat configuration. Other tropanes having a 3 β -oriented group are of the chair configuration.

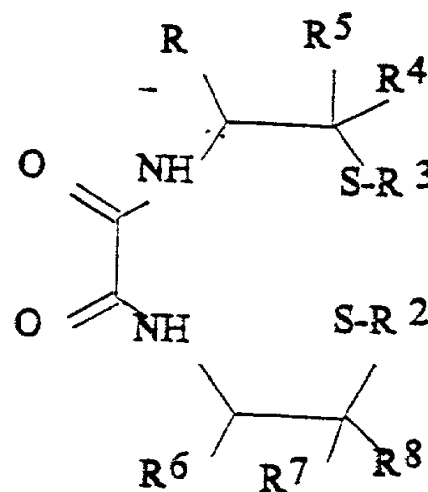
Chelating ligands useful in the practice of the present invention comprise any tridentate or tetradentate ligand that binds technetium or rhenium to form a neutral complex. The chelating ligand is covalently attached to the linker L, as described below. Preferred chelating ligands contain a plurality of N or S atoms for complexing with the radionuclide.

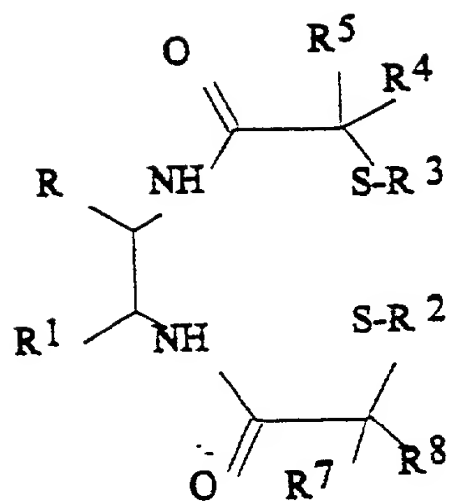
Examples of suitable ligands are the N₂S₂ compounds represented by the following structural formulas:



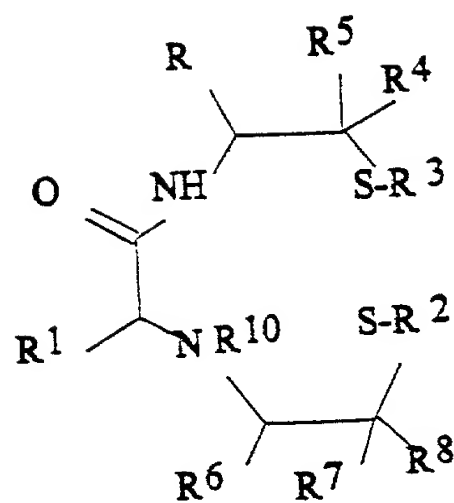
III

IV

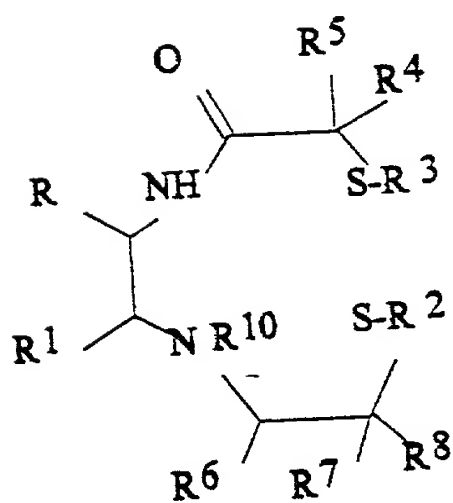




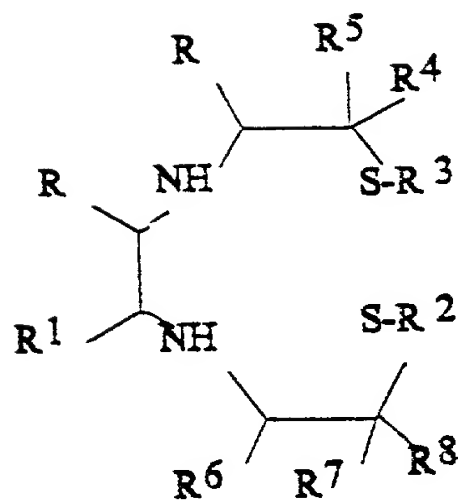
V



VI



VII



VIII

wherein R, R⁶, and R¹⁰ are each selected from hydrogen, substituted or unsubstituted lower alkyl, alkylR⁹, or -COR⁹ where R⁹ is selected from hydroxy, substituted lower alkoxy, substituted or unsubstituted amino, glycine ester, halide (chloro, bromo, iodo) or OR (OR is a leaving group such as mesylate, triflate, or tosylate) or an activated leaving group; R¹ is selected from hydrogen, or substituted or unsubstituted lower alkyl; R² and R³ are each selected from hydrogen or a thiol protecting group, or an inter or intramolecular disulfide; and R⁴, R⁵, R⁷ and R⁸ are each selected from hydrogen or lower alkyl.

When R, R⁶ or R¹⁰ is a carboxylic acid derivative, R⁹ can be an activated leaving group. For purposes of this invention the leaving group R⁹ is defined such that (compound)-COR⁹ is an acylating agent. Examples of activated leaving groups suitable for the practice of this invention include, for example: halide; substituted or unsubstituted aryloxy groups such as phenoxy, pentachlorophenoxy, etc.; oxyheterocyclic groups such as N-oxy-succinimido, etc.; mercapto; lower alkylthio; arylthio; oxyphosphonium; and other groups known to those skilled in the art to be useful as leaving groups.

R² and R³ can be hydrogen or any known thiol protecting group. Examples of such groups include lower alkylaminocarbonyl such as ethylaminocarbonyl, lower alkanoylaminomethyl, aroylaminomethyl, t-butyl, acetamidomethyl, arylmethyl such as triphenylmethyl (trityl) and diphenylmethyl, aroyl such as benzoyl, aryloxycarbonyl such as phenoxycarbonyl, arylloweralkoxycarbonyl, preferably arylmethoxycarbonyl,

benzyloxycarbonyl, and lower alkoxycarbonyl such as t-butoxycarbonyl. Preferred thiol protecting groups include trityl, t-butyl, diphenylmethyl, acetamidomethyl and benzoyl and an inter or intramolecular disulfide.

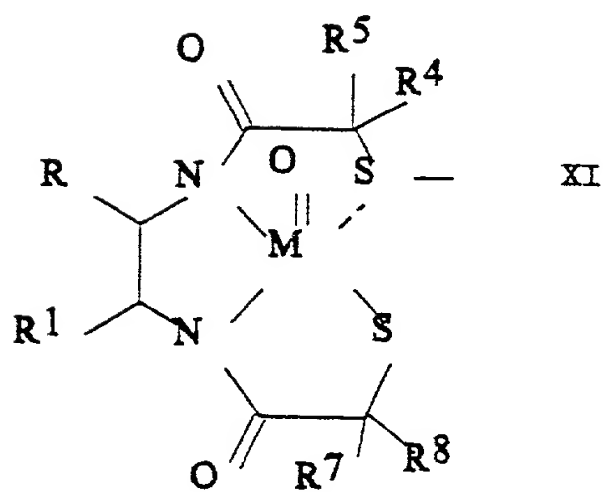
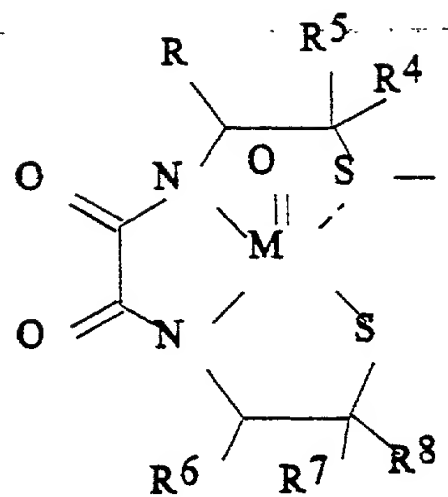
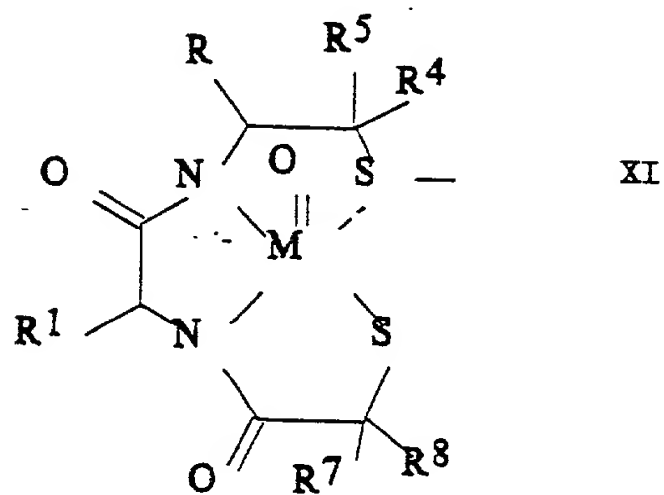
5 The term "lower alkyl" when used herein designates aliphatic saturated branched or straight chain hydrocarbon monovalent substituents containing from 1 to 6 carbon atoms such as methyl, ethyl, isopropyl, n-propyl, n-butyl, etc., more preferably 1 to 4 carbons. The term "lower alkoxy" designates lower alkoxy substituents containing from 1 to 6 carbon atoms such as methoxy, ethoxy, isopropoxy, etc., more preferably 1 to 4 carbon atoms.

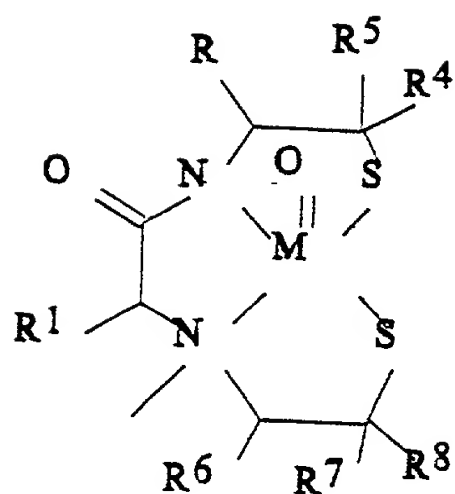
10 The terms substituted lower alkyl or substituted lower alkoxy when used herein include alkyl and alkoxy groups substituted with halide, hydroxy, carboxylic acid, or carboxamide groups, etc. such as, for example, -CH₂OH, -CH₂CH₂COOH, -CH₂CONH₂, -OCH₂CH₂OH, -OCH₂COOH, -OCH₂CH₂CONH₂, etc.

15 The term substituted amino when used herein includes such groups mono or di and tri-substituted with lower alkyl, and -NH₃⁺ or mono, di and tri-substituted ammonium groups substituted with lower alkyl with a pharmacologically suitable anion.

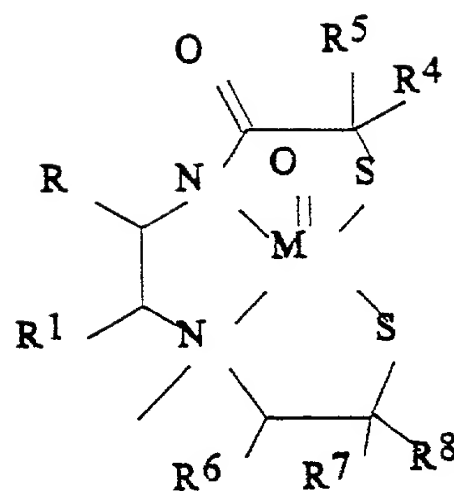
20 The term glycine ester as used herein means the lower alkyl esters of glycine, preferably the methyl and ethyl esters.

These chelating ligands can be complexed with a radionuclide, e.g., technetium, to form the following complexes:

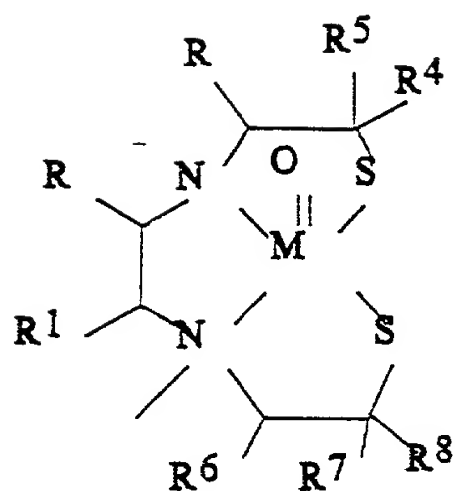




XII



XIII



XIV

where the R groups are defined as above.

Preferred embodiments of the invention use chelating ligands that are formed from monoaminomonoamide compounds having structures of formula V, VI or VII, e.g., *N*-{2-((2-((triphenylmethyl)-thio)-ethyl)amino)acetyl)-*S*-(triphenylmethyl)-2-aminoethanethiol ("MAMA").

5

Any organic linker having a backbone chain length of 1 to about 6 carbon atoms can be used to attach the chelating ligand, typically through its nitrogen, sulfur, R, R¹ or R⁶, to the 8-nitrogen atom of the tropane ligand (which binds the dopamine transporter). Examples of linkers include -(CH₂)_n where n is an integer from 1 to 6, or -(CH₂)_n - (aryl, arylalkyl, ethenyl or ethynyl) - (CH₂)_m where the sum of n plus m is an integer from 1 to 6.

10

Preferred radiolabeled compounds of the present invention cross the blood brain barrier and exhibit desired target:non-target specificity. Preferably, the selectivity ratio of binding (DAT:SET) is about 30 or more, more preferably 50 or more. Thus, they are useful as brain imaging agents, for example, for imaging DAT.

15

The tropane ligands can be linked to the chelating ligand by an initial conversion to nortropanes. Syntheses of nortropanes are known in the art, for example, as disclosed in Meltzer, P.C., et al., *J. Med. Chem.* 1993, 36, 855-862; Meltzer, P.C., et al., *J. Med. Chem.* 1994, 37, 2001-2010 (the disclosure of which is incorporated herein by reference). Tropanes can be synthesized from tropinone or cocaine by techniques known in the art. Synthesis of the nortropanes can then be achieved by N-demethylation of the tropane, which can be readily accomplished by

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various methods known in the art, e.g., with α - chloroethyl chloro formate (ACE-Cl).

The chelating ligand is preferably prepared separately and, then, either attached to the nortropane and metallated, or metallated first followed by attachment to the appropriate nortropane. When the radiolabeled compounds of the invention are required to cross the blood brain barrier, the chelating ligands useful in the present invention form neutral complexes with the radionuclide and are lipid soluble.

Chelating ligands that form neutral $^{99m}\text{Tc(V)}$ complexes which are useful in the present invention include a substituted oxime (Loberg, M.D., et al., *J. Nucl. Med.* 1979, 20, 1181-1188), N_2S_2 compounds (Davison, A., et al., *Inorg. Chem.* 1981, 20, 1629-1632; Davison, A., et al., *J. Nucl. Med.* 1979, 20, 641 (abstr)), bisaminoethanethiol ("BAT") (Kung, H.F., et al., *J. Med. Chem.* 1985, 28, 1280-1284; Kung, H.F., et al., *J. Nucl. Med.* 1986, 27, 1051; Kung, H.F., et al., *J. Med. Chem.* 1989, 32, 433-437; Kung, H.F., et al., *J. Nucl. Med.* 1984, 25, 326-332; Francesconi, L.C., et al., *Inorg. Chem.* 1993, 32, 3114-3124), and diaminodithiol ("DADT") (Lever, S.Z., et al., *J. Nucl. Med.* 1985, 26, 1287-1294). Additional examples of useful chelating ligands include N,N'-bis(2-mercapto-1-methyl)-2-aminobenzylamine ("U-BAT") (Francesconi, L.C., et al., *J. Med. Chem.* 1994, 37, 3282-3288), propylene amine oximes ("HMPAO"), diamidodithiol ("DADS") (Rao, T.N., et al., *J. Am. Chem. Soc.* 1990, 112, 5798-5804; Stepniak-Biniakiewicz, D., et al., *J. Med. Chem.* 1992, 35, 274-279), phenylenediamine-thiol-thioether ("PhAT") (McBride, B.J., et al., *J. Med. Chem.* 1993, 36, 81-86), bis(mercaptoethyl)-2-aminoethylamine ("SNS") or bis(mercaptoethyl)-2-thioethylamine (Mastrostamatis, S.G., et al., *J. Med. Chem.* 1994, 37, 3212-3218), monoamine amide ("MAMA") (Gustavson, L.M., et al., *Tet. Lett.* 1991, 32, 5485-5488)

and *N*-{2-((2-((triphenylmethyl)thio)ethyl)amino)acetyl}-*S*-(triphenylmethyl)-2-aminoethanethiol ("MAMA") (O'Neil, J.P., et al., *Inorg. Chem.* 1994, 33, 319-323). For example, when MAMA' is attached to a lipophilic tropane by a linker in accord with the present invention, a neutral, moderately lipophilic and aqueous stable compound
5 suitable for radiolabeling is formed.

Compounds of formula III and IV can be synthesized according to the methods described in U.S. Patent No. 4,673,562 which is incorporated herein by reference. Compounds of formula V can be synthesized by methods known in the art (see
10 Fritzberg et al., *J. Nucl. Med.* 1981, 22, 258-263). Compounds of formula VI can also be synthesized by methods known in the art. (See O'Neil, J.P., et al., *Inorg. Chem.* 1994, 33, 319-323).

Radiolabeled complexes of the present invention can be prepared via three
15 general preparation procedures as outlined in the General Scheme (FIG. 1). The general preparation scheme exemplifies the use of trityl protecting groups for the sulfhydryls, however, other protecting groups that are known to be useful for sulfhydryl protection can also be used such as, for example, lower alkylaminocarbonyl such as ethylaminocarbonyl, lower alkanoylaminomethyl, arylaminomethyl, *t*-butyl, acetamidomethyl, arylmethyl such as triphenylmethyl(trityl) and diphenylmethyl, aryl
20 such as benzoyl, aryloxycarbonyl such as phenoxycarbonyl, aryl loweralkoxycarbonyl, preferably arylmethoxycarbonyl such as benzyloxycarbonyl, and lower alkoxycarbonyl such as *t*-butoxycarbonyl. Preferred sulfhydryl protecting groups include trityl, *t*-butyl, diphenylmethyl, acetamidomethyl, disulfide and benzoyl.

The compounds of the invention can be prepared by known means based upon the present disclosure. For example, starting with an appropriate chelating ligand, such as an N_2S_2 compound, illustrated in the general scheme in FIG. 1 as *N*-{2-((2-
5 ((triphenylmethyl)thio)ethyl)amino)acetyl}-*S*-(triphenylmethyl)-2-aminoethanethiol, (MAMA': Katzenellenbogen et al., *Inorg. Chem.*, 1994, 33, 319), the N_2S_2 compound can be alkylated with either the haloalkyl triflate or the haloalkylnortropane (prepared from the nortropane: Meltzer et al., *J. Med. Chem.*, 1993, 36, 855), producing the chloroalkyl (propyl shown) MAMA', or the tropanalkyl (propyl shown) MAMA',
10 compounds, respectively. The chloroalkyl (propyl shown) MAMA' compound, can then be attached to a suitable nortropane to provide the tropanalkyl (propyl shown) MAMA' compounds, as shown. Alternatively, the chloroalkyl (propyl shown) MAMA', can be treated to incorporate a metal atom, preferably a radionuclide (such as ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{188}Re or ^{186}Re) to provide the M-labeled complex. The resulting complex can then be
15 attached to a suitable nortropane to provide radiopharmaceutical compounds of the present invention, as shown.

Alternatively, the tropanalkyl (propyl shown) MAMA' compounds, can be treated to incorporate a radionuclide (such as ^{99}Tc , $^{99\text{m}}\text{Tc}$, ^{188}Re or ^{186}Re) to form
20 radiopharmaceutical compounds of the present invention, as shown.

The compounds of the present invention can be either diastereoisomer as well as a mixture of both diastereomers. The diastereoisomers can be separated by column chromatography.

More specifically, alkylation of the N₂S₂, with haloalkyl triflate to produce the chloroalkyl (propyl shown) MAMA', can be used to prepare the linker which is used to bind the chelating ligand to the tropane ligand, which selectively binds the dopamine transporter. This alkylation step can be modified by those of ordinary skill in organic chemistry to create various linkers having a backbone chain length of 1 to about 6 carbon atoms, as described above.

Deprotection of the chloroalkyl compound can be accomplished by standard methods well known in the art, e.g., with H₂S/Hg(OAc)₂ (O'Neil, J.P., et al., *Inorg. Chem.* 1994, 33, 319-323) or AgNO₃/Py (DiZio, J.P., et al., *Bioconj. Chem.* 1991, 2, 353-366), with TFA and phenol, or HBr in acetic acid (Zervas, L., et al., *J. Amer. Chem. Soc.* 1962, 84, 3887-3897) to result in the unprotected bisthiol which can then be immediately treated with a solution of tin (II) chloride (SnCl₂) and sodium perrhenate (Na₂ReO₇) or an agent such as Na(^{99m}TcO₄)/stannous tartrate (Francesconi, L.C., et al., *Inorg. Chem.* 1993, 32, 3114-3124; Canney, D.J., et al., *J. Med. Chem.* 1993, 36, 1032-1040) to produce the labeled complexes. Purification of these chelates can be accomplished by flash chromatography as described by O'Neil (O'Neil, J.P., et al., *Inorg. Chem.* 1994, 33, 319-323). The chloroalkyl chelate, can then be reacted (O'Neil, J.P., et al., *Bioconj. Chem.* 1994, 5, 182-193) with the appropriate nortropane to provide the labeled coordination complexes of the present invention. Alkylation of nortropanes can be accomplished by methods known in the art, e.g., acetonitrile (CH₃CN), potassium iodide (KI) and potassium carbonate (K₂CO₃). The use of strong base can cause epimerization of the carbomethoxy group at C-2, although sodium

carbonate in a solvent such as dimethyl formamide (DMF) can yield alkylated products in reasonable yield.

These compounds can be prepared either as free bases or as a
5 pharmacologically active salt thereof such as hydrochloride, tartrate, sulfate, naphthalene-1,5-disulfonate or the like.

Reaction schemes for preparation of various classes of compounds of the present invention are described with reference to the drawings. In Scheme 1, as
10 illustrated in FIG. 2, Keto ester **1** {Meltzer et al., *J. Med. Chem.*, 1994, **37**, 2001} is converted to the enol triflate **2** by reaction with N-phenyltrifluoromethanesulfonimide and sodium bis(trimethylsilyl)amide in tetrahydrofuran. The enol triflate **2** is then coupled with the appropriate commercial or preformed arylboronic acids by Suzuki
coupling in diethoxymethane in the presence of lithium chloride, sodium carbonate and tris(dibenzylideneacetone)dipalladium(0) to provide aryl octenes **3** in excellent
15 yield.

Reduction of the octenes **3** with samarium iodide in tetrahydrofuran/methanol at low temperature (-78 °C) provides a mixture of the 3 β - and 3 α - diastereomers, **4**
20 and **12** respectively. These diastereomers are readily separated by flash column chromatography.

In Scheme 7, as illustrated in FIG. 8, the 3 β - and 3 α - diastereomers **4** and **12** are then treated similarly in their conversion to the bistrityl protected N₂S₂ tropanes

33 and **36** respectively and thence to the rhenium analogs **34R** and **37R** and the technetium analogs **34T** and **37T**. Thus, the tropanes are N-dealkylated by treatment with ACE-chloride {Meltzer et al., *J. Med. Chem.*, 1993, **36**, 855} to provide the nortropanes **32** and **35**. Introduction of the N₂S₂ protected, ligand is then achieved
5 by reaction of the nortropanes with the preformed N-[[[2-[2-(triphenylmethyl)thio]-ethyl](N'-3'-chloropropyl)amino]acetyl]-S-(triphenylmethyl)-2-aminoethanethiol (MAMA'-Cl){Meltzer et al. *J. Med. Chem.*, **40**, 1835, 1997} in the presence of potassium iodide and potassium carbonate. Rhenium can then be introduced upon reaction with tin (II) chloride in 0.05 M HCl, followed by sodium perrhenate in 0.05 M HCl.
10 The product is purified by silica gel column chromatography and obtained as a mixture of diastereomers. An alternative approach utilizes N-alkylation of the nortropanes with preformed N-[(2-((3'-chloropropyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethane-thiolato]rhenium (V) oxide {Meltzer et al. *J. Med. Chem.*, **40**, 1835, 1997}. Both diastereomers of the metal chelate are prepared.

15 In Schemes 2 and 3, as illustrated in FIGs. 3 and 4, the 2-ethylketo analogs in both the 3 α - and 3 β - series are prepared as shown. This discussion exemplifies the 3 β -diastereomer, as illustrated in FIG. 3. The 3 β -diastereomer **4** is hydrolyzed in dioxane/water or with lithium hydroxide to provide the acid, **5** which is converted to
20 the amide through conversion to the acid chloride with oxalyl chloride and then reaction with (MeO)MeNH.HCl to provide **6**. Further reaction with alkyl Grignard at low temperature provides the desired ethyl or alkyl ketone **7**. The alkyl ketone **7** can be made alternatively by reaction of the ester-tropane (**4** or **12**) with the appropriate alkyl-Grignard-(ethylmagnesium bromide in this case) (Ref: I. Kikkawa and T. Vorifuji,

Synthesis (1980), p. 877). Demethylation is by standard treatment with ACE-Cl to obtain **8**. The chelating unit is attached by reaction of **8** with MAMA'-Cl in the presence of a base such as potassium carbonate or potassium bicarbonate and potassium iodide. Insertion of rhenium to provide **10** or technetium to provide **11** is accomplished with sodium perrhenate under reductive conditions, of the technetium heptogluconate. Both diastereomers of the metal chelate can be prepared in a similar manner. As seen by comparing Schemes 2 and 3, the 3 α - diastereomer of the tropane is prepared in a similar manner.

In Scheme 4, as illustrated in FIG. 5, the 2-carboxamide analogs **22** and **22A** are prepared from **14** by N-demethylation with ACE-Cl as described earlier. Attachment of the MAMA' group and insertion of the metal (rhenium or technetium) is conducted as described earlier for Schemes 2 and 3.

In Scheme 5, as illustrated in FIG. 6, the 2-ethylketo trop-2-ene analogs are prepared as shown in the scheme. Thus, ester **3** is hydrolyzed in dioxane/water or with lithium hydroxide to provide the acid **23** which is converted to the amide through conversion to the acid chloride with oxalyl chloride and then reaction with (MeO)MeNH.HCl to provide **24**. Further reaction with alkyl Grignard at low temperature provides the desired ethyl or alkyl ketone **25**. The alkyl ketone **25** can be formed alternatively by reaction of the ester tropene (**3**) with the appropriate alkyl-Grignard-(ethylmagnesium bromide) (Ref: I. Kikkawa and T. Vorifuji, *Synthesis* (1980), p. 877). Demethylation is by standard treatment with ACE-Cl to obtain **26**. The chelating unit is attached by reaction of **26** with MAMA'-Cl in the presence of a base

such as potassium carbonate or potassium bicarbonate and potassium iodide. Insertion of rhenium or technetium to provide **28** is accomplished with sodium perrhenate under reductive conditions of the technetium heptogluconate. Both diastereomers of the metal chelate **28** are prepared.

5

In Scheme 6, as illustrated in FIG. 7, the 2-carbomethoxy trop-2-ene analogs are prepared as shown in the scheme. Demethylation of compound **3** is by standard treatment with ACE-Cl to obtain compound **29**. The chelating unit is attached by reaction of compound **30** with MAMA'-Cl in the presence of a base such as potassium carbonate or potassium bicarbonate and potassium iodide. Insertion of rhenium or technetium to provide compound **31** is accomplished with sodium perrhenate under reductive conditions, of the technetium heptogluconate. Both diastereomers of the metal chelate **31** are prepared.

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In Scheme 8, as illustrated in FIG. 9, the 2-ethylketo trop-2-ene analogs are prepared as shown in the scheme. Thus, compound **3** is reduced with LAH and reoxidized to obtain the aldehyde **39**. Reaction of the aldehyde with ethyl lithium or ethyl Grignard provides the alcohol **40** which is oxidized once again to obtain the ethyl ketone **26**. Compounds **27** and **28** are then obtained as above.

20

In Scheme 9, as illustrated in FIG. 10, the 3-naphthyl trop-2-ene and 3 α - and 3 β -tropanes are obtained by similar chemistry to that described earlier. Thus, the trop-2-ene **38** is N-demethylated with ACE-Cl and the MAMA' is attached to provide compound **40**. Rhenium or technetium are inserted as before to obtain the

diastereomers **41**. Alternatively, compound **38** is first reduced with samarium iodide to obtain both the boat and chair configured compounds **43** and **42**. The same sequence of reactions then provides the rhenium and technetium diastereomers of both the 3 α - and 3 β -tropanes, **49** and **48**.

5

The technetium or rhenium radionuclide complexes of this invention can be formed by reacting suitable precursor compounds with either pertechnetate or perrhenate in the presence of a suitable reducing agent in a conventional manner. For example, the compound can be dissolved in a suitable solvent with a reducing agent and then pertechnetate added. The mixture is then heated for a suitable length of time to complete the reaction. Typically, heating in a boiling water bath for about 10 minutes has been found sufficient to obtain very good yields of the radionuclide complex. To form rhenium complexes, (Ph₃P)₂ReOCl₃ is added in the presence of basic (NaOAc) methanol. Examples of reducing agents useful in the practice of this invention include stannous salts such as stannous chloride, sodium dithionite, and ferrous salts such as ferrous sulfate.

Rhenium behaves similarly to Tc. Thus, N₂S₂ complexes of Re or Tc are equally stable. Both metals form square pyramidal complexes with N₂S₂ ligands. (Francesconi, L.C., et al., *Inorg. Chem.* 1993, 32, 3114-3124). Rhenium is a preferred metal for use in studies which do not require the presence of a short half life radiolabel. For complexes with both technetium and rhenium, the oxygen occupies an apical position, therefore both syn and anti-isomers of the metal complexes are possible. The biological activity of Tc and Re chelates are generally similar. (O'Neil,

J.P., et al., *Bioconjugate Chem.* 1994, 5, 182-193). ^{99m}Tc is a preferred radionuclide for use as an imaging agent. Rhenium is an excellent model for ^{99m}Tc and is also useful as a therapeutic agent.

5 A preferred method for introducing the technetium radionuclide was by reaction of the bistrityl protected compounds in presence of anhydrous trifluoroacetic acid and then triethylsilane. A portion of the aqueous solution thus obtained was then incubated with ^{99m}Tc -glucoheptonate solution (Glucoscan kits from Du Pont, Billerica, MA). HPLC separation on a C8 reverse phase column equipped provides the
10 major ^{99m}Tc labeled product which was reconstituted in sterile saline for injection.

The compounds of this invention are typically enantiomerically pure tropanes (either 1S or 1R configuration) attached by an achiral linker to a chiral chelating ligand. The chiral chelating ligand can be *cis* or *trans* with respect to the metal oxo
15 and the linker, but is preferably *cis*. Each of the *cis* and *trans* chelating ligands exist as a pair of two enantiomers. By virtue of the chiral ligand which can exist in each of two enantiomeric forms, and a chiral tropane, each of the whole molecules exists as diastereoisomers. Radiopharmaceutical compositions of the present invention include the separate diastereoisomers of each, as well as mixtures of diastereomeric pairs.

20 The compounds of the present invention preferably have a target:nontarget ratio, such as a DAT:SET selectivity ratio of greater than 10, and preferably at least 30, to minimize binding of trace levels of the drug to the nontarget, e.g., serotonin transporter.

The present invention also provides pharmaceutical kits, preferably comprising the compounds of formula I with a reducing agent in lyophilized form in a pyrogen-free, sterilized container or vial. In this form the lyophilized composition can be readily reconstituted by adding only water, saline, or a buffer preferably having a pH in the range of 5 to 8, more preferably physiological pH. If technetium is the metal to be used as the radionuclide, pertechnetate solution from a technetium generator can be used for reconstitution.

In general, the radiopharmaceutical preparation kit comprises a sterilized unit dose (or multidose) vial containing the purified compound of formula I and a reducing agent for technetium, preferably lyophilized. Each dose should consist of a sufficient amount of compound and reducing agent to prepare the required dose for imaging, normally about 5 to about 30 mCi of ^{99m}Tc depending upon body weight of the mammal to be imaged. In use, the technetium, preferably as ^{99m}Tc -pertechnetate in saline, is injected aseptically into the vial and the mixture reacted for a sufficient time to form the labeled complex. After reaction, typically, the resulting radiopharmaceutical is ready for use.

To image a desired target, a radiopharmaceutical preparation in accord with this invention having an effective dose of radioactivity for the particular mammal is prepared in a suitable pharmacological carrier, such as normal saline. Preferably, the radiopharmaceutical preparation is injected intravenously into the mammal. The target, e.g., the brain, is then imaged by positioning the mammal under a gamma

camera or other suitable device.

In order to obtain high quality images, the radiochemical yield of bound technetium in the desired radiopharmaceutical should preferably be greater than 70% after reconstituting the lyophilized mixture and labelling. Lower yields may result in poorer image quality and undesirable purification steps may be required to produce high quality images.

This invention will be illustrated further by the following examples. These examples are not intended to limit the scope of the claimed invention in any manner.

The final compounds were characterized and their purity analyzed prior to biological evaluation. High field nuclear magnetic resonance (NMR) spectra were measured as well as low and high resolution mass spectra (MS) and infrared spectra (IR). Elemental analyses, thin layer chromatography (TLC) and/or high performance liquid chromatography (HPLC) were used as a measure of purity. A purity of >98% was obtained before biological evaluation of these compounds was undertaken.

In the following examples, NMR spectra were recorded on either a Bruker 100, a Varian XL 400, or a Bruker 300, or a Jeol 300 NMR spectrometer. TMS was used as internal standard. Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus. Optical rotations were measured at the sodium D line at 21°C using a JASCO DIP 320 polarimeter (1dcm cell). Thin layer chromatography (TLC) was carried out on Baker Si 250F plates. Visualization was

accomplished with either iodine vapor, UV exposure or treatment with phosphomolybdic acid (PMA). Preparative TLC was carried out on Analtech uniplates Silica Gel GF 2000 microns. Flash chromatography was carried out on Baker Silica Gel 40 M (SiO₂). Elemental Analyses were performed by Atlantic Microlab, Atlanta, GA. A Beckman 1801 Scintillation Counter was used for scintillation spectrometry. 0.1% Bovine Serum Albumin and (-)-Cocaine were purchased from Sigma Chemicals. All reactions were conducted under an atmosphere of dry nitrogen.

[³H]WIN 35,428 and 2β-carbomethoxy-3β-(4-fluorophenyl)-N-[³H]methyltropine (79.4-87.0 Ci/mmol), and [³H]citalopram (86.8 Ci/mmol) were purchased from DuPont-New England Nuclear (Boston, MA). TEA is triethylamine. (-)-Cocaine hydrochloride for the pharmacological studies was donated by the National Institute on Drug Abuse [NIDA]. Fluoxetine was donated by E. Lilly & Co. HPLC analyses were carried out on a Waters 510 system with detection at 254 nm on a Waters 8 mm, C-18, 10 m reverse phase column. Pd₂dba₃ is trisdibenzylideneacetone dipalladium, TFA is trifluoroacetic acid, THF is tetrahydrofuran, EtOAc is ethyl acetate.

EXAMPLE 1: (1*R*)-2-(Methoxycarbonyl)-3-[[trifluoromethyl)sulfonyl]oxy]-trop-2-ene (Compound **2**, FIG. 2)

(1*R*)-(-)-2-Methoxycarbonyl-3-tropinone, **1** {Meltzer et al., *J. Med. Chem.*, 1994, **37**, 2001}(1 g, 5.07 mmol) was dissolved in anhydrous THF (20 mL) and the resulting solution cooled to -78 °C. A solution of sodium bistrimethylsilylamide (1 M, 5.58 mL, 5.58 mmol) was then added to the solution slowly. After 30 min, N-phenyltrifluoro-

methane sulfonamide (1.94 g, 5.43 mmol) was added. The resulting solution stirred for a further 45 min at -78 °C and then allowed to attain room temperature and stirred at room temperature for 2h. All solvent was evaporated and the residue pumped to dryness. Column chromatography was performed on the residue (SiO₂ 60 g; 2%-16% methanol in ethyl acetate) and gave 1.62 g (97%) of a yellow oil which crystallized on standing.

R_f 0.65 (10% MeOH/EtOAc). ¹H-NMR (CDCl₃) δ 1.58 (m, 1H), 1.97 (m, 2H), 2.1-2.2 (m, 2H), 2.39 (s, 3H). 2.84 (dd, J=18, 4Hz, 1H), 3.42 (t, J=6Hz, 1 H), 3.8 (s, 3H), 3.92 (d, J=5Hz, 1H).

EXAMPLE 2: (1*R*)-N-Methyl-2-methoxycarbonyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]oct-2-ene (Compound **3**, FIG. 2)

(1*R*)-2-Methoxycarbonyl-3-[[[(trifluoromethyl)sulfonyl]oxy] tropene **2** (620 mg, 1.88 mmol), LiCl (171 mg, 4.03 mmol), Pd₂dba₃ (69 mg, 0.075 mmol), aq. Na₂CO₃ (2.0 M, 2 mL), diethoxymethane (6.2 mL) were all charged to a flask and stirred vigorously. To this solution was added 3,4-dichlorophenyl boronic acid (474 mg, 2.49 mmol). The reaction was then brought to reflux for 2h and filtered through celite. The cake was washed with ether and the organic solution was washed with concentrated NH₄OH. The washed solvent was dried with K₂CO₃, filtered, and evaporated. The residue was charged to a column (SiO₂, 60 g, eluted with 5-6% Et₃N/EtOAc) and gave 512 mg (83%) of a yellow oil which solidified upon standing.

R_f 0.56 (10% Et₃N/EtOAc). IR (KBr) 2941, 1724, 1460, 1418, 1333, 1250, 1212, 1124
cm⁻¹. ¹H-NMR (CDCl₃) δ 1.61 (m, 1H), 1.9-2.05 (m, 2H), 2.1-2.3 (m, 2H), 2.43 (s, 3H),
2.76 (dd, J=19, 4.7 Hz, 1H), 3.36 (t, J=4.9Hz, 1H), 3.52 (s, 3H), 3.86 (d, J=5.5 Hz, 1H),
6.96 (dd, J=8.3, 1.9 Hz, 1H), 7.2 (d, J=2.2Hz, 1H), 7.37 (d, J=8.2 Hz, 1H). Elemental
analysis: calculated C, 58.91, H, 5.25, N, 4.29; found C, 58.84, H, 5.24, N, 4.24.

EXAMPLE 3: (1*R*)-N-Methyl-2β-methoxycarbonyl-3β-(3,4-dichlorophenyl)-8-
azabicyclo[3.2.1]octane (Compound **4** (R=3,4-Cl₂), FIG. 2),
and
(1*R*)-N-Methyl-2β-methoxycarbonyl-3α-(3,4-dichlorophenyl)-8-
azabicyclo[3.2.1]octane (Compound **12** (R=3,4-Cl₂), FIG. 2)

To (1*R*)-N-Methyl-2-methoxycarbonyl-3-(3,4-dichlorophenyl)-8-aza-
bicyclo[3.2.1]oct-2-ene, **3** (4 g, 12.3 mmol) in THF (43 mL) at -78 °C was added SmI₂
solution (0.1 M in THF, 400 mL, 40 mmol) dropwise. After 30 min at -78 °C, MeOH
(140 mL) was added and the resulting solution stirred at -78 °C for a further 1h. The
reaction was then quenched with TFA (28 mL) and water (285 mL), the cold bath was
removed and the solution allowed to attain room temperature. The reaction was then
made basic with NH₄OH and diluted with ether and filtered through celite. The filter
cake was washed with ether and all the organic phases were combined and washed
with a sodium thiosulfate solution and then a brine solution. After drying with
Na₂SO₄ the solution was filtered and concentrated and gave 3.8 g of the crude
products. The title compounds **4** and **12** were isolated by column chromatography
(SiO₂, 10 g; 2.5% EtOH in CHCl₃). Compound **12** was isolated as colorless crystals

(1.15 g, 29%).

Mp. 89-91 °C. R_f 0.64 (1% NH₄OH/EtOAc). ¹H-NMR (CDCl₃) δ 1.28 (ddd, J=1.6, 10.4, 14, 1H), 1.4-1.6 (m, 2H), 2.23 (s, 3H), 2.05-2.3 (m, 2H), 2.35-2.5 (m, 2H), 3.2-3.47 (m, 3H), 3.59 (s, 3H), 7.04 (dd, J=2.2, 8.2Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.30 (d, J=8.2 Hz, 1H). Elemental analysis: calculated (0.1 C₆H₁₄) C, 59.18, H, 6.10, N, 4.16, Cl, 21.05; found C, 59.11, H, 5.90, N, 4.08, Cl, 21.01.

Compound **4** (R=3,4-Cl₂) (Meltzer et al., *J. Med. Chem.*, 1993, **36**, 855-862) was isolated as a yellow solid (1.04 g, 26%).

Mp. 82.5-83.5 °C. R_f 0.43 (IPA/Et₂O/pentane; 3/30/67); ¹H NMR (400MHz, CDCl₃) δ 1.6-1.7 (m, 3H), 2.0-2.1 (m, 2H), 2.21 (s, 3H), 2.50 (ddd, 1H, H-4), 2.86(m, 1H), 2.92 (m, 1H), 3.33 (m, 1H, H-5), 3.52 (s, 3H), 3.55 (m, 1H), 7.07-7.32 (m, 3H). [α]_D²¹ -27.0° (c=1, CH₃OH). Anal. (C₁₆H₁₉NO₂Cl₂) C, H, N, Cl.

EXAMPLE 4: (1*R*)-N-Methyl-2β-methoxycarbonyl-3β-(4-fluorophenyl)-8-azabicyclo[3.2.1]octane (Compound **4** (R=4-F), FIG. 2)
and
(1*R*)-N-Methyl-2β-methoxycarbonyl-3α-(4-fluorophenyl)-8-azabicyclo[3.2.1]octane (Compound **12** (R=4-F), FIG. 2; O-1204)

Using the same general procedure as described above for Example 3, except substituting (1*R*)-N-Methyl-2-methoxycarbonyl-3-(4-fluorophenyl)-8-aza-

bicyclo[3.2.1]oct-2-ene, **3**, compounds **4** and **12** (R=4-F) were obtained.

Compound **4** (R=4-F) : white solid; Mp 93-94 °C;

R_f 0.42 (i-PrNH₂:Et₂O:pentane::5:30:65); ¹H-NMR (400 MHz, CDCl₃) δ 1.57-1.75 (m,

5 3H), 2.0-2.2 (m, 2H), 2.23 (s, 3H), 2.54 (ddd, 1H), 2.84 (t, 1H), 2.95 (ddd 1H, J=5.3, 12.7 Hz), 3.36 (m, 1H), 3.50 (s, 3H), 3.55 (m, 1H), 6.9-7.25 (m, 4H). [α]_D²¹ -45.6° (c=1, CH₃OH). Anal. (C₁₆H₂₀NO₂F) C, H, N.

Compound **12** (R=4-F) : colorless oil;

10 R_f 0.5 (10% MeOH in EtOAc); Elemental analysis: calculated C, 69.29 , H, 7.27 , N, 5.05; found C, 69.35 , H, 7.26, N, 5.00; IR 2900, 1750, 1500 cm⁻¹, ¹H-NMR (100 MHz, CDCl₃) δ 1.1-1.8 (m, 4H), 1.9-2.6 (m, 3H), 2.25 (s, 3H), 3.1-3.7 (m, 3H), 3.59 (s, 3H), 6.8-7.3 (m, 4H).

15 EXAMPLE 5: 2β-Carboxy-3β-(4-fluorophenyl)tropane
(Compound **5** (R=4-F), FIG. 3)

20 2β-Methoxycarbonyl-3β-(4-fluorophenyl)tropane (WIN 35,428), **4** (1.25 g, 4.54 mmol) was refluxed for 24 h in a 1:1 dioxane-water (80 mL) solution. The solvent was removed in vacuo and the residue was almost completely dissolved in CHCl₃ (275 mL). Remaining undissolved solid was filtered off, toluene (30 mL) was added, and the solution was reduced in vacuo by approximately 75%. After cooling the resulting white suspension in the freezer for 2 h, the white solid was removed by filtration and was washed with cold 1:1 CHCl₃-toluene. The solid was pumped dry to yield the

product **5** as a white solid (1.11 g, 95%).

¹H-NMR (CDCl₃) δ 1.7-1.8 (m, 1H), 1.94 (dd, J=9 Hz, 2H) 2.24-2.34 (m, 2H), 2.25 (m, 3H), 2.57 (ddd, J=13.7 Hz, 1H), 2.62-2.68 (m, 1H), 3.16 (ddd, J=13 Hz, 1H), 3.5-3.6 (m, 2H), 6.8 (m, 2H), 7.18-7.24 (m, 2H).

EXAMPLE 6: 2β-Carboxy-3β-(3,4-dichlorophenyl)tropane
(Compound **5** (R=3,4-Cl₂), FIG. 3)

2β-Methoxycarbonyl-3β-(3,4-dichlorophenyl)tropane, **4** (1.14 g, 3.47 mmol) was dissolved in THF:MeOH (1:1; 46 mL) to which was added a solution of LiOH.H₂O (153 mg) in water (11 mL). The solution was heated to reflux for 24h, cooled to 0 °C and neutralized (pH=7) with conc. HCl. Silica (1.75 g) was added directly to the solution and solvent was removed in vacuo. The material was purified by flash chromatography column (eluent 20% MeOH/CHCl₃ (900 mL) followed by 30% MeOH/CHCl₃ (2 L)). Fractions containing the product were collected and combined, evaporated in vacuo and the residue was dried at high vacuum. The product was obtained (310 mg; 28%).

R_f 0.08 (30% MeOH/CHCl₃); ¹H-NMR (CDCl₃) δ 1.8-1.9 (m, 1H), 2.1-2.2 (m, 2H) 2.3-2.5 (m, 2H), 2.6-2.9 (m, 2H), 2.78 (s, 3H), 3.3-3.4 (m, 1H), 3.93 (m, 2H), 7.25 (dd, J=8.2 Hz, 2.2 Hz, 1H), 7.41 (d, J=8.2 Hz, 1H), 7.48 (d, J=2.2 Hz, 1H).

EXAMPLE 7: 2 β - Methoxymethylcarbamoyl -3 β -(4-fluorophenyl)tropane
(Compound **6** (R=4-F), FIG. 3)

To a stirred suspension of the acid **5** (1.1 g) in anhydrous CH₂Cl₂ (80 mL) containing DMF (50 μ L) was added oxalyl chloride (1 mL, 11.4 mmol) dropwise resulting in copious bubbling and dissolution of the suspension. The reaction was allowed to stir for 45 min during which time the solution became yellow. The solution was then reduced in vacuo and pumped at high vacuum overnight, care being taken to bleed nitrogen into the evacuated flask when transferring from the rotary to the pump.

To the acid chloride dissolved in CH₂Cl₂ (80 mL) was added (MeO)MeNH HCl (450 mg; dried immediately prior to use over P₂O₅ under high vacuum followed immediately by pyridine (1.1 mL). The reaction was allowed to stir for 1h and was partitioned across CHCl₃ (20 mL) and 2M Na₂CO₃ (20 mL). The aqueous layer was extracted CHCl₃ (2 x 10 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and reduced in vacuo to yield 1.09 g of a yellow solid. The crude product was dissolved in CH₂Cl₂ and purified by flash chromatography (SiO₂, 43 g; 20% hexanes/EtOAc, 5% Et₃N). Product containing fractions were combined and concentrated to yield a light yellow solid **6** (960 mg; 75%).

Mp. 120.1-122.5 °C; R_f 0.14 (25% hexanes /EtOAc, 5% TEA); Elemental analysis: calculated C, 66.65 , H, 7.57 , N, 9.14 ; found C, 66.78 , H, 7.63 , N, 9.01; IR (KBr) 2900, 1680, 1500 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.5-1.8 (m, 3H), 2.0-2.3 (m, 2H), 2.24 (m, 3H), 2.79 (ddd, 1H), 3.0 (m, 1H), 3.05 (s, 3H), 3.1 (m, 1H), 3.4 (m, 1H), 3.47 (m, 1H),

3.57 (s, 3H), 6.9 (m, 2H), 7.25 (m, 2H).

EXAMPLE 8: 2β-Methoxymethylcarbamoyl-3β-(3,4-dichlorophenyl)tropane
(Compound **6** (R=3,4-Cl₂), FIG. 3)

5 To a stirred solution of 2β-carboxy-3β-(3,4-dichlorophenyl)tropane, **5** (300 mg, 9.55 mmol) in anh. CH₂Cl₂ (30 mL) was added anh. DMF (40 μL) and oxalyl chloride (450 μL) dropwise. The solution was stirred at room temperature for 40 min. The solvent was removed in vacuo and the residue dried at high vacuum overnight.

10 To the dry residue was added methoxy methylamine hydrochloride (103 mg, 1.05 mmol). The flask was flushed with nitrogen and CH₂Cl₂ (30 mL) was added by cannula followed immediately by pyridine (400 μL). The reaction was stirred for 2.5h. The resultant mixture was partitioned between CH₂Cl₂ (40 mL) and 1M Na₂CO₃ (25 mL). The aqueous layer was extracted with CHCl₃ and the combined organic extracts were dried and concentrated to yield a yellow solid (298 mg). The solid was purified
15 on a chromatography column (eluent 50% EtOAc/hexane/5% Et₃N). Like fractions were combined, solvent removed and the product dried at high vacuum to yield Compound **6** (39 mg; 11%).

R_f 0.1 (50% EtOAc/hexane/5% Et₃N); ¹H-NMR (CDCl₃) δ 1.5-1.74 (m, 3H), 2.0-2.3
20 (m, 2H), 2.21 (m, 3H), 2.72 (ddd, 1H), 2.93 (m, 1H), 3.04 (s, 3H), 3.13 (m, 1H), 3.38 (m, 1H), 3.5 (m, 1H), 3.62 (s, 3H), 7.13 (dd, 1H), 7.30 (d, 1H), 7.31 (d, 1H).

EXAMPLE 9: 2 β -(1-Propanoyl)-3 β -(4-fluorophenyl)tropane

(Compound **7** (R=4-F), FIG. 3)

A solution of 2 β -(N-methoxy-N-methylcarbamoyl)-3 β -(4-fluorophenyl)-tropane, **6** (823 mg, 2.7 mmol) in THF (10 mL) was cooled to 0 °C and EtMgBr/Et₂O (3M; 3 mL) was added dropwise over 4 min. The reaction was warmed to room temperature for 30 min and then heated to 65 °C for 45 min. The mixture was cooled to 0 °C and quenched by addition of ethereal HCl (3M). The resulting cloudy solution was basified with 2M Na₂CO₃. Ether (5 mL) was added and the layers separated and the aqueous layer washed with Et₂O (1 x 10 mL) and CHCl₃ (2 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The product was purified by flash column chromatography (eluent 25% EtOAc/hexanes/5% TEA) to provide **7** (485 mg, 65 %).

R_f 0.3 (20% EtOAc/hexanes/5% Et₃N); mp 118-119.5 °C; Elemental analysis: calculated C, 74.15 , H, 8.05, N, 5.09; found C, 74.05, H, 8.09, N, 5.00. IR (KBr) 2900, 1710, 1500. 1250 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.85 (t, 3H), 1.5-1.8 (m, 4H), 2.0-2.4 (m, 3H), 2.23 (m, 3H), 2.5-2.6 (m, 1H), 2.9-3.0 (m, 2H), 3.36 (m, 1H), 3.48 (m, 1H), 6.69 (m, 2H), 7.17 (m, 2H).

EXAMPLE 10: 2 β -(1-Propanoyl)-3 β -(3,4-dichlorophenyl)tropane

(Compound **7** (R=3,4-Cl₂), FIG. 3)

A solution of 2 β -methoxymethylcarbamoyl-3 β -(3,4-dichlorophenyl), **6** (168 mg, 0.47 mmol) in THF (30 mL) was cooled to 0 °C and EtMgBr/Et₂O (3M; 1 mL) was

added dropwise over 3 min. The reaction was warmed to room temperature for 60 min and then heated to reflux for 10 min. The mixture was cooled to room temperature and quenched by addition to ethereal HCl (3M, 20 mL). The resulting cloudy solution was basified with saturated aqueous NaHCO₃ and brought to pH=10 by addition of Na₂CO₃. Ether was added and the layers separated and the aqueous layer washed with Et₂O (3 x 25 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated. The product (166 mg) was purified by flash column chromatography (eluent 30% EtOAc/hexanes/5% Et₃N) to provide **7** (108 mg, 71%).

R_f 0.32 (50% EtOAc/hexanes/5% Et₃N); ¹H-NMR (CDCl₃) δ 0.9 (t, 3H), 1.5-1.8 (m, 4H), 2.0-2.3 (m, 3H), 2.2 (m, 3H), 2.35-2.55 (m, 2H), 2.82-2.92 (m, 1H), 2.96 (m, 1H), 3.34 (m, 1H), 3.54 (m, 1H), 7.75 (dd, 1H), 7.27 (d, 1H), 7.29 (d, 1H).

EXAMPLE 11: 2β-(1-Propanoyl)-3β-(4-fluorophenyl)nortropane
(Compound **8** (R=4-F), FIG. 3)

2β-(1-Propanoyl)-3β-(4-fluorophenyl)tropane, **7** (335 mg) was combined with 1-chloroethyl chloroformate (5 mL) and the solution was heated to reflux for 5h. The excess chloroformate was removed in vacuo and the residue was refluxed in methanol for 1.5h. The methanol was removed in vacuo and the residue was dissolved in CHCl₃ (15 mL) and shaken with 2M Na₂CO₃. The aqueous layer was extracted CHCl₃ (2 x 15 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated to yield 369 mg. This residue was chromatographed (eluent: 100

mL EtOAc, 150 mL 5% Et₃N/EtOAc, 100 mL 10% Et₃N/EtOAc, 300 mL 20% Et₃N/EtOAc, and 300 mL 30% Et₃N/EtOAc). Like fractions were combined to yield **8** (104 mg, 33%).

5 R_f 0.36 (10% Et₃N/EtOAc); ¹H-NMR (CDCl₃) δ 0.70 (t, 3H), 1.4-1.8 (m, 5H), 1.9-2.3 (m, 3H), 2.4 (m, 1H), 2.88 (m, 1H), 3.18 (m, 1H), 3.56 (m, 1H), 3.70 (m, 1H), 6.94 (m, 2H), 7.10 (m, 2H).

EXAMPLE 12: 2β-(1-Propanoyl)-3β-(3,4-dichlorophenyl)nortropane
10 (Compound **8** (R=3,4-Cl₂), FIG. 3)

2β-(1-Propanoyl)-3β-(3,4-dichlorophenyl)tropane **7** (107 mg, 0.32 mmol) was combined with 1-chloroethyl chloroformate (2 mL) and the solution was heated to reflux for 5h. The excess chloroformate was removed in vacuo and the residue was refluxed in methanol for 45 min. The methanol was removed in vacuo and the
15 residue was dissolved in CH₂Cl₂ and shaken with NaHCO₃/Na₂CO₃ (pH=9). The aqueous layer was extracted CH₂Cl₂ (4 x 10 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated to yield 127 mg. This residue was chromatographed (1 x 100 mL 5% Et₃N/EtOAc; 3 x 100 mL 10% Et₃N/EtOAc). Like fractions were combined to yield **8** (30 mg, 29%).

20 ¹H-NMR (CDCl₃) δ 0.76 (t, 3H), 1.4-2.5 (m, 9H), 2.92 (m, 1H), 3.09-3.2 (m, 1H), 3.6 (m, 1H), 3.72 (m, 1H), 7.0 (m, 1H), 7.25 (d, 1H), 7.32 (d, 1H).

EXAMPLE 13: N-[2-(3'-N'-Propyl-(1''*R*)-3''β-(4-fluorophenyl)tropane-2''β-(1-propanoyl))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (Compound **9** (R=4-F), FIG. 3) (O-1507)

5 2β-(1-Propanoyl)-3β-(4-fluorophenyl)nortropane **8** (27 mg) was combined with MAMA'-Cl (86 mg), KI (34 mg, 2.0 eq.), and NaHCO₃ (43 mg, 5 eq.) in anhydrous MeCN (4 mL) and brought to reflux for 4h. The solvent was removed under vacuum and the residue was partitioned between CHCl₃ and saturated aqueous NaHCO₃. The aqueous layer was extracted CHCl₃ (2 x 5 mL) and the combined organic extracts
10 were dried (Na₂SO₄), filtered and concentrated to yield a brown foam. The foam was applied to a chromatography column (10 g silica; 40% EtOAc in hexanes/1% TEA). Fractions containing the product were combined and concentrated to yield **9** as a light foam (47 mg, 46%).

15 R_f 0.09 (60% EtOAc/hexanes, 1% Et₃N). Elemental analysis: calculated C, 72.15, H, 6.34, N, 3.96; found C, 71.99, H, 6.41, N, 3.92. ¹H-NMR (CDCl₃) δ 0.77 (t, 3H), 1.2-3.1 (m, 29H), 3.3-3.5 (m, 2H), 6.9-7.0 (m, 2H), 7.1-7.6 (m, 32H).

EXAMPLE 14: N-[2-(3'-N'-Propyl-(1''*R*)-3''β-(3,4-dichlorophenyl)tropane-2''β-(1-propanoyl))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (Compound **9** (R=3,4-Cl₂), FIG. 3)

20 2β-(1-Propanoyl)-3β-(3,4-dichlorophenyl)nortropane **8** (30 mg, 0.096 mmol) was combined with MAMA'-Cl (87 mg, 0.115 mmol, 1.2 eq.), KI (32 mg, 0.19 mmol, 2.0

eq.), and NaHCO₃ (40 mg, 0.48 mmol, 5 eq.) in anhydrous MeCN (4 mL) and brought to reflux for 4h then cooled to room temperature and allowed to stir overnight. The solvent was removed under vacuum and the residue was partitioned between CH₂Cl₂ (15 mL) and saturated aqueous NaHCO₃ (15 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated to yield a yellow oil (115 mg). The oil was applied to a chromatography column (10 g SiO₂; 30% EtOAc in hexanes/1% Et₃N). Fractions containing the product were combined and concentrated to yield **9** as a light foam (41 mg, 41%).

R_f 0.14 (60% EtOAc/hexanes, 1% Et₃N). ¹H-NMR (CDCl₃) δ 0.81 (t, 3H), 1.2-3.1 (m, 29H), 3.34 (m, 1H), 3.52 (m, 1H), 7.0-7.6 (m, 33H).

EXAMPLE 15: N-[(2-((3'-N'-Propyl-(1''R)-3''β-(4-fluorophenyl)tropane-2''β-1-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethane-thiolato]rhenium (V) oxide (Compound **10** (R=4-F), FIG. 3) (O-1508R)

N-[2-(3'-N'-Propyl-(1''R)-3''β-(4-fluorophenyl)tropane-2''β-(1-propanoyl))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (22 mg, 0.023 mmol) was dissolved in boiling EtOH (abs. 4 mL) and SnCl₂ (8.5 mg, in 0.5 mL of 0.05M HCl). The reaction was maintained at reflux for a further 6h and silica was added and the solvents removed by evaporation. The silica adsorbed product was applied to a silica column (3g eluent: 30% EtOAc in hexanes with 5% Et₃N). The

compound was obtained as a foam (6.7 mg, 44%).

R_f 0.07 (60% EtOAc in hexanes + NH₄OH (0.5%)) Accurate Mass calc for

C₂₅H₃₅FN₃O₃ReS₂ : 695.172; found 695.162. ¹H-NMR (CDCl₃) δ 0.7-0.9 (2t, 2H),

5 1.4-4.1 (m, 26H), 4.5-4.6 (m, 1H), 4.73 (d, J=16.5 Hz, 0.5H) 4.87 (d, J=16.5 Hz, 0.5H),
6.93 (m, 2H), 7.14 (m, 2H).

EXAMPLE 16: 2β-(Carboxylic acid)-3α-(4-fluorophenyl)tropane

(Compound **13** (R=4-F), FIG. 4)

10 A solution of 2β-methoxycarbonyl-3α-(4-fluorophenyl)-tropane **12** (1.0 g, 3.6
mmol) was refluxed for 24h in 80 mL dioxane water (1:1). The solvent was removed in
vacuo and the brown solid was purified by column chromatography (eluent 30%
MeOH/CHCl₃). The product (890 mg, 94%) was obtained as a white foam.

15 R_f 0.43 (30% MeOH/CHCl₃); NMR ¹H-NMR (CDCl₃) δ 1.48-1.62 (m, 1H), 1.75-2.1 (m,
3H), 2.36-2.46 (m, 1H), 2.60 (s, 3H), 2.7-2.82 (m, 1H), 3.22 (brs, 1H), 3.5-3.62 (m, 2H),
3.76-3.84 (m, 1H), 6.9-7.1 (m, 2H), 7.4-7.5 (m, 2H).

EXAMPLE 17: 2β-(Carboxylic acid)-3α-(3,4-dichlorophenyl)tropane

20 (Compound **13** (R=3,4-Cl₂), FIG. 4)

A solution of 2β-methoxycarbonyl-3α-(3,4-dichlorophenyl)tropane **12** (750 mg,
2.29 mmol) and LiOH (335 mg, 8.0 mmol) was brought to reflux for 4h in water (10
mL) and THF:MeOH (33 mL; 1:1). The reaction was neutralized by dropwise addition

of conc. HCl. The solvent was removed in vacuo and the product purified by column chromatography (eluent 15% MeOH/CHCl₃). The product **13** (521 mg, 72 %) was obtained as a solid.

5 R_f 0.15 (30% MeOH/CHCl₃); ¹H-NMR (CD₃OD) δ 1.59 (m, 1H), 1.8-1.9 (m, 1H), 2.1-2.2 (m, 2H), 2.6-2.7 (m, 2H), 2.76 (s, 3H), 3.25 (brs, 1H), 3.35 (brs, 1H), 3.85 (m, 1H), 3.93 (m, 1H), 7.5 (d, 1H), 7.53 (dd, 1H), 7.8 (d, 1H).

EXAMPLE 18: 2β-Methoxymethylcarbamoyl-3α-(4-fluorophenyl)tropane
10 (Compound **14** (R=4-F), FIG. 4) (O-1403)

To a stirred suspension of Compound **13** (930 mg, 3.6 mmol) in anhydrous CH₂Cl₂ (80 mL) containing DMF (50 μL) was added oxalyl chloride (1 mL, 11.4 mmol) dropwise resulting in copious bubbling and dissolution of the suspension. The reaction was allowed to stir for 45 min during which time the solution became yellow.
15 It was then reduced in vacuo and pumped at high vacuum overnight, care being taken to bleed nitrogen into the evacuated flask when transferring from the rotary to the pump.

To the acid chloride dissolved in CH₂Cl₂ (70 mL) was added (MeO)MeNH•HCl (382 mg, 3.9 mmol) followed immediately by pyridine (1 mL). The reaction was
20 allowed to stir for 1h and then partitioned between CHCl₃ (20 mL) and 2M Na₂CO₃ (20 mL). The aqueous layer was extracted with CHCl₃ (2 x 10 mL) and the combined organic extracts were dried over Na₂SO₄, filtered and reduced in vacuo to yield a yellow oil. The oil was dissolved in toluene and concentrated to yield a yellow solid

(653 mg). The crude product was dissolved in a minimum volume of CHCl_3 , and applied to a chromatography column (28 g SiO_2 ; eluent 25% hexanes in EtOAc, 5% Et_3N ; followed by 25% MeOH in CHCl_3). Product containing fractions were combined and concentrated to yield the amide (540 mg; 50%).

5

R_f 0.25 (25% hexanes/EtOAc, 5% Et_3N); mp. 139.8-141.7 °C; $^1\text{H-NMR}$ (CDCl_3) δ 1.24 (dd, 1H), 1.4-1.8 (m, 3H), 2.1-2.3 (m, 2H), 2.23 (s, 3H), 2.4-2.6 (m, 1H), 2.7 (brd, 1H), 3.05 (s, 3H), 3.05-3.1 (m, 1H), 3.25-3.5 (m, 2H), 3.41 (s, 3H), 6.86-6.96 (m, 2H), 7.13-7.22 (m, 2H); IR (KBr) 2900, 1656, 1500 cm^{-1} . Elemental analysis: calculated C, 66.65, H, 7.57, N, 9.14; found C, 66.37, H, 7.59, N, 9.0.

10

EXAMPLE 19: 2 β -Methoxymethylcarbamoyl-3 α -(3,4-dichlorophenyl)tropane
(Compound **14** (R=3,4- Cl_2), FIG. 4)

15

To a stirred suspension of the acid **13** (210 mg, 0.67 mmol) in anhydrous CH_2Cl_2 (10 mL) containing DMF (30 μL) was added oxalyl chloride (0.3 mL, 2.0 mmol) dropwise. The reaction was allowed to stir for 1h and then reduced in vacuo and pumped at high vacuum overnight, care being taken to bleed nitrogen into the evacuated flask when transferring from the rotary to the pump.

20

To the acid chloride in CH_2Cl_2 (10 mL) was added (MeO)MeNH. HCl (72 mg, 0.74 mmol) followed immediately by pyridine (0.3 mL). The reaction was allowed to stir for 1.5h and was partitioned between CH_2Cl_2 (10 mL) and 1M Na_2CO_3 solution (5 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) and the combined organic extracts were dried over Na_2SO_4 , filtered and reduced in vacuo to yield a

yellow solid. The solid was purified by column chromatography (14 g SiO₂, eluent 25% hexanes/EtOAc, 5% Et₃N). Product containing fractions were combined and concentrated to yield the amide (115 mg; 48%).

5 R_f 0.14 (40% hexanes/EtOAc, 5% Et₃N); ¹H-NMR (CDCl₃) δ 1.17 (ddd, 1H), 1.48 (ddd, 1H), 1.63 (ddd, 1H), 2.1-2.34 (m, 2H), 2.21 (s, 3H), 2.42-2.54 (m, 1H), 2.65 (brd, 1H), 3.06 (s, 3H), 3.08 (brs, 1H), 3.22-3.32 (m, 1H), 3.34-3.46 (m, 1H), 3.48 (s, 3H), 7.05 (dd, 1H), 7.25 (d, 1H), 7.27 (d, 1H).

10 EXAMPLE 20: 2β-(1-Propanoyl)-3α-(4-fluorophenyl)-tropane
(Compound **15** (R=4-F), FIG. 4) (O-1369)

A 250 mL round bottom flask containing the 2β-methoxymethylcarbamoyl-3α-(4-fluorophenyl)tropane **14** (471 mg) was flushed with nitrogen and charged with anhydrous THF (70 mL). At room temperature, EtMgBr/Et₂O (3.0 mL; 3.0M) was added dropwise over 3 min. The reaction was stirred at room temperature for 30 min and was then heated to 65°C for 1h at which point no starting material was observed by TLC (TLC sample was prepared by adding an aliquot of the reaction to ethereal HCl, and basifying with 2M Na₂CO₃; R_f (product) 0.42; R_f (starting material) 0.13 (20% EtOAc/hexanes, 5% Et₃N). The reaction was cooled in an ice bath and
20 quenched by slow addition of ethereal HCl. The cloudy solution was basified with 2M Na₂CO₃ and diluted with ether (25 mL). The layers were separated and the aqueous layer was extracted with ether (1 x 10 mL) and CHCl₃ (2 x 20 mL). The combined organic extracts were dried (Na₂SO₄), filtered and reduced in vacuo to yield the crude

residue (484 mg). This residue was then chromatographed (25 g SiO₂; eluent 25% EtOAc/hexanes, 5% Et₃N). Fractions containing the product were combined and concentrated to yield **15** (300 mg, 70%);

5 Mp. 60.5-61.3 °C; R_f 0.49 (33% EtOAc/hexanes; 5% Et₃N); ¹H-NMR (CDCl₃) δ 0.86 (t, 3H), 1.27 (ddd, 1H), 1.4-1.6 (m, 2H), 2.0-2.5 (m, 6H), 2.23 (s, 3H), 3.12 (brd, 1H), 3.2-3.3 (m, 2H), 6.85-7.0 (m, 2H), 7.05-7.15 (m, 2H); IR (KBr) 2900, 1740, 1500 cm⁻¹; Elemental analysis: calculated C, 74.15, H, 8.05, N, 5.09; found C, 74.00, H, 8.13, N, 4.98

10
EXAMPLE 21: 2β-(1-Propanoyl)-3α-(3,4-dichlorophenyl)tropane
(Compound **15** (R=3,4-Cl₂), FIG. 4)

2β-Methoxymethylcarbamoyl-3α-(3,4-dichlorophenyl)tropane, **14** (105 mg, 0.29 mmol) was flushed with nitrogen and charged with anhydrous THF (15 mL). At room temperature, EtMgBr/Et₂O (0.8 mL; 3.0M) was added dropwise over 3 min. The reaction was stirred at room temperature for 1h and was then heated to 55°C for 30 min at which point no starting material was observed by TLC. The reaction was cooled in an ice bath and quenched by slow addition of ethereal HCl. The cloudy solution was basified with 2M Na₂CO₃ and diluted with ether (15 mL) and water (15 mL). The layers were separated and the aqueous layer was extracted with CHCl₃ (2 x 15 mL). The combined organic extracts were dried (Na₂SO₄), filtered and reduced in vacuo to yield a residue (95 mg) which was chromatographed (5 g SiO₂, eluent 25% EtOAc in hexanes, 5% Et₃N). Fractions containing the product were combined and

concentrated to yield **15** (80 mg, 80%).

R_f 0.28 (30% EtOAc/hexanes; 5% Et₃N); ¹H-NMR (CDCl₃) 0.93 (t, J=7.4Hz, 3H),
1.27 (ddd, 1H), 1.42-1.62 (m, 2H), 2.06-2.30 (m, 6H), 2.21 (s, 3H), 3.32-2.52 (m, 3H),
5 3.14 (brd 1H), 3.2-3.36 (m, 2H), 7.10 (dd, 1H), 7.24 (d, 1H), 7.29 (d, 1H).

EXAMPLE 21a: 2β-(1-Propanoyl)-3α-(3,4-dichlorophenyl)tropane
(Compound **15** (R-3,4-Cl₂), FIG. 4)

To commercially available ethylmagnesium bromide (1M in THF, 12.6 mL, 12.6
10 mmol) in a flask equipped with an addition funnel under nitrogen was added
triethylamine (5.0 g, 50.4 mmol). To the resulting mixture was added drop-wise a
solution of compound **12** (R=Cl₂, 750 mg, 2.29 mmol) in benzene (10 mL) at 5-10°C
over a period of 1 hour. The reaction mixture was then stirred at 5-10°C for 5 hours
and then treated with 4 M HCl (2.9 mL, 11.6 mmol). The organic layer was washed
15 with water (1 x 50 mL), 5% NaHCO₃ (aq) (1 x 50 mL) and water (2 x 50 mL). The
organic phase was then dried (K₂CO₃), filtered and the concentrated. The residue was
chromatographed (SiO₂. 25% EtOAc in hexanes with 5% Et₃N) and gave 670 mg (85%)
of compound **15** with the same physical and spectral characteristics as previously
reported (Example 21).

20
EXAMPLE 22: 2β-(1-Propanoyl)-3α-(4-fluorophenyl)nortropane
(Compound **16** (R=4-F), FIG. 4) (O-1370)

2β-(1-Propanoyl)-3α-(4-fluorophenyl)tropane **15** (O-1369) (556 mg, 2 mmol) and
ACE-Cl (7 mL) were combined and brought to reflux for 4h. All volatiles were removed

by evaporation and methanol (100 mL) was added to the residue. The resulting mixture was brought to reflux for 90 min. Volatiles were removed and the residue was taken up in CHCl₃ and washed with aq. 2M Na₂CO₃. The aqueous mixture was extracted with CHCl₃ (2 x 10 mL) and organic fractions combined, dried (Na₂SO₄),
5 filtered and reduced. The dark brown oil (615 mg) was chromatographed (SiO₂, 20 g; 0 -10% Et₃N in EtOAc) and gave 390 mg (74%) of a yellow oil.

R_f 0.25 (5% Et₃N in EtOAc); ¹H-NMR (CDCl₃) δ 0.86 (t, 3H), 1.27 (ddd, 1H), 1.50-1.72 (m, 2H), 1.8-2.1 (m, 3H), 2.2-2.4 (m, 2H), 2.56 (dd, J=10.7, 1Hz, 1H), 3.07 (ddd, J=11.3, 10.9, 7.1Hz, 1H), 3.43 (brd 1H), 3.62 (brt, 1H), 6.89-6.99 (m, 2H), 7.09-7.16 (m, 2H). IR (KBr) 2900, 1711, 1500 cm⁻¹; Elemental analysis: calculated (0.2 H₂O) C, 72.52, H, 7.77, N, 5.25; found C, 72.65, H, 7.81, N, 5.27

EXAMPLE 23: 2β-(1-Propanoyl)-3α-(3,4-dichlorophenyl)nortropane
(Compound **16** (R=3,4-Cl₂), FIG. 4)

2β-(1-Propanoyl)-3 -(3,4-dichlorophenyl)tropane, **15** (80 mg, 2.45 mmol) was combined with 1-chloroethyl chloroformate (3 mL) and the solution was heated to reflux for 5h. The excess chloroformate was removed in vacuo and the residue was refluxed in methanol for 1h. The methanol was removed in vacuo and the residue
20 was dissolved in CHCl₃ and washed with 2M Na₂CO₃. The aqueous layer was extracted with CHCl₃ (2 x 5 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated to yield pure compound (77 mg; 100%).

R_f 0.3 (5% Et₃N/EtOAc); ¹H-NMR (CDCl₃) δ 0.91 (t, 3H), 1.25 (ddd, 1H, 1.52-1.74 (m, 2H), 1.8-2.56 (m, 7H), 3.06-3.2 (m, 1H), 3.45 (d, 1H), 3.62 (brt, 1H), 7.01 (dd, 1H), 7.25 (d, 1H), 7.31 (d, 1H).

5. EXAMPLE 24: N-[2-(3'-N'-Propyl-(1''R)-3''α-(4-fluorophenyl)tropane-2''β-(1-propanoyl))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (compound **17** (R=4-F), FIG. 4) (O-1506)

2β-(1-Propanoyl)-3α-(4-fluorophenyl)nortropane **16** (24 mg, 0.09 mmol), MAMA'-Cl (147 mg, 0.19 mmol), KI (31 mg, 19 mmol) were all dissolved in CH₃CN (3 mL) and brought to reflux for 3h. Solvent was removed in vacuo and the residue partitioned between satd. aq NaHCO₃ and CHCl₃. The aqueous layer was further extracted with CHCl₃, all organic fractions were combined and dried (Na₂SO₄), filtered and concentrated. Column chromatography (20% EtOAc, 79% Hexane, 1% Et₃N) gave pure product as a golden foam (11.5 mg, 13%).

R_f 0.15 (50% EtOAc in hexanes + 5% Et₃N); Elemental analysis: calculated (0.1H₂O) C, 75.79, H, 6.87, N, 4.21; found C, 75.35, H, 6.81, N, 4.13. ¹H-NMR (CDCl₃) δ 0.85 (t, 3H), 1.19 (ddd, 1H), 1.3-1.5 (m, 6H), 1.8-2.6 (m, 14H), 2.85 (brs, 2H), 3.0 (m, 2H), 3.08-3.30 (m, 3H), 6.88-6.96 (m, 2H), 7.06-7.42 (m, 32H).

EXAMPLE 25: N-[2-(3'-N'-Propyl-(1''*R*)-3'' α -(3,4-dichlorophenyl)tropane-2'' β -(1'''-propanoyl))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (Compound **17** (R=3,4-Cl₂), FIG.4) (O-1546)

5 2 β -(1-Propanoyl)-3 α -(3,4-dichlorophenyl)nortropane **16** (75 mg, 0.24 mmol) was combined with N'-(((2-(2-(triphenylmethyl) thio)ethyl)(N'-3'-chloropropyl)amino)-acetyl)-S-(triphenylmethyl)-2-aminoethanethiol (MAMA'-Cl) (218 mg, 0.29 mmol), KI (80 mg, 0.48 mmol), and NaHCO₃ (101 mg, 1.2 mmol) in anhydrous MeCN (20 mL) and brought to reflux for 4h then cooled to room temperature. The solvent was removed under vacuum and the residue was partitioned between CH₂Cl₂ (20 mL) and saturated aqueous NaHCO₃ (15 mL). The aqueous layer was extracted with CH₂Cl₂ (1 x 10 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated to yield a brown oil. The oil was applied to a chromatography column (30 g SiO₂; eluent: 25% EtOAc/hexanes/1% Et₃N). Fractions containing the product were combined and concentrated to yield **17** (51 mg, 17%).

R_f 0.3 (60% EtOAc in hexanes, 1% Et₃N); Elemental analysis: calculated (1.33 H₂O) C, 71.71, H, 6.46, N, 3.98; found C, 71.85, H, 6.52, N, 3.91. ¹H-NMR (CDCl₃) δ 0.89 (t, 3H), 1.0-1.7 (m, 8H), 1.8-2.5 (m, 14H), 2.6-3.4 (m, 6H), 6.9-7.6 (m, 33H).

EXAMPLE 26: N-[(2-((3'-N'-Propyl-(1''R)-3'' α -(4-fluorophenyl)tropane-2'' β -1'''-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethane-thiolato]rhenium (V) oxide (Compound **18** (R=4-F), FIG. 4) (O-1505)

5 A solution of N-[2-(3'-N'-Propyl-(1''R)-3'' α -(4-fluorophenyl)tropane-2'' β -(1'''-propanoyl))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol, **17** (22 mg) in EtOH (4 mL) was heated to reflux. A solution of SnCl₂ (7.8 mg, 0.04 mmol) in 0.005 M HCl (0.5 mL) was added quickly followed immediately by NaReO₄ (12.4 mg, 0.04 mmol) in 0.005 M HCl (0.5 mL). The cloudy
10 solution was refluxed for 6h and was then loaded onto 0.5 g silica and pumped overnight. The silica-adsorbed material was applied to a chromatography column (3 g SiO₂; eluent 30% EtOAc/hexanes/5% TEA). The purple brown solid obtained was triturated with pentane and dried at high vacuum overnight to yield **18** as a foam (9.9 mg; 71%).

15 Accurate Mass calc 695.161 (found, 695.172). R_f 0.30 (75% EtOAc in hexane + 0.5% NH₄OH); ¹H-NMR (CDCl₃) δ 0.75-0.95 (2t, 3H), 1.0-2.0 (m, 8H), 2.0-2.5 (m, 6H), 2.8-3.0 (m, 1H), 3.0-3.5 (m, 7H), 3.6-3.8 (m, 1H), 3.9-4.2 (m, 3H), 4.5-4.65 (m, 1H), 4.73, 5.12 (2d, J=16.7Hz), 6.9-7.0 (m, 2H), 7.08-7.15 (m, 2H).

EXAMPLE 27: N-[(2-((3'-N'-Propyl-(1''R)-3'' α -(3,4-dichlorophenyl)tropane-2'' β -1'''-propanoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethane-thiolato]rhenium (V) oxide (Compound **18** (R=3,4-Cl₂), FIG. 4)

A solution of N-[2-(3'-N'-Propyl-(1''R)-3'' α -(3,4-dichlorophenyl)tropane-2'' β -(1-
5 propanoyl))(2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol, **17**, (24 mg, 0.024 mmol) in EtOH (5 mL) was heated to reflux. A solution of SnCl₂ (9 mg, 0.05 mmol) in 0.005 M HCl (0.5 mL) was added quickly followed immediately by NaReO₄ (14.5 mg, 0.05 mmol) in 0.005 M HCl (0.5 mL). The solution was refluxed for 4h and was then loaded onto 0.5 g silica and pumped at
10 high vacuum overnight. The silica-adsorbed material was applied to a chromatography column (4 g SiO₂; eluent 30% EtOAc/hexanes/5% Et₃N). The solid obtained was concentrated to yield **18** (4.6 mg; 27%).

¹H-NMR (CDCl₃) δ 0.8-1.0 (2t, 3H), 1.1-2.5 (m, 14H), 2.8-3.0 (m, 1H), 3.0-3.5 (m, 7H),
15 3.6-3.8 (m, 1H), 3.9-4.2 (m, 3H), 4.4-4.65 (m, 1H), 4.70, 5.06 (2d, 2xJ=16.7Hz, 1H), 7.0 (dd, 1H), 7.3 (d, 1H), 7.34 (d, 1H).

EXAMPLE 28: 2 β -(Methoxymethylcarbamoyl-3 α -(4-fluorophenyl)nortropane
(compound **20** (R=4-F), FIG. 5)

20 2 β -(1-Propanoyl)-3 α -(4-fluorophenyl)tropane **14** (112 mg, 0.37 mmol) was combined with 1-chloroethyl chloroformate (2.2 mL) and the solution was heated to reflux for 5h. The excess chloroformate was removed in vacuo and the residue was refluxed in methanol for 45 min. The MeOH was removed in vacuo and the residue

was dissolved in CHCl_3 and $\text{NaHCO}_3/\text{Na}_2\text{CO}_3$ (pH=9). The aqueous layer was extracted CHCl_3 (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated to yield 104 mg. This residue was chromatographed (eluent: 10-20% Et_3N in EtOAc). Like fractions were combined to yield **20** (65 mg, 60%).

5

R_f 0.13 (10% Et_3N in EtOAc); $^1\text{H-NMR}$ (CDCl_3) δ 1.30 (ddd, 1H), 1.5-1.75 (m, 2H), 1.85-2.15 (m, 2H), 2.2-2.35 (m, 1H), 2.7-2.9 (m, 1H), 3.05 (s, 3H), 3.1-3.22 (m, 1H), 3.38 (s, 3H), 3.4-3.5 (m, 1H), 3.6-3.7 (m, 1H), 6.9-7.0 (m, 2H), 7.13-7.23 (m, 2H).

10

EXAMPLE 29: N-[2-(3'-N'-Propyl-(1''R)-3'' α -(4-fluorophenyl)tropane-2'' β -(methoxymethylcarbamoyl))((2-((triphenylmethyl)thio)ethyl)-amino)acetyl]-S-(triphenyl)-2-aminoethanethiol
(Compound **21** (R=4-F), FIG. 5) (O-1450)

15

2 β -(1-Propanoyl)-3 α -(4-fluorophenyl)nortropane **20** (65 mg, 0.22 mmol) was combined with MAMA'-Cl (203 mg, 0.27 mmol, 1.2 eq.), KI (74 mg, 0.45 mmol), and K_2CO_3 (309 mg, 2.2 mmol) in anhydrous MeCN (10 mL) and brought to reflux for 6h then cooled to room temperature. The solvent was removed under vacuum and the residue was partitioned between CHCl_3 and water. The aqueous layer was extracted with CHCl_3 (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated to yield a yellow oil which was applied to a chromatography column (15 g SiO_2 eluent 120 mL of 50% EtOAc /hexanes/5% Et_3N). Fractions containing the product were combined and concentrated to yield **21** as a light yellow oil (142 mg, 41%).

20

R_f 0.7 (5% Et₃N/EtOAc); Elemental analysis: calculated (0.3H₂O) C, 71.02, H, 6.96, N, 5.26; found C, 71.20, H, 6.45, N, 5.14. ¹H-NMR (CDCl₃) δ 1.2-3.5 (m, 24H), 2.85 (s, 2H), 3.02 (s, 3H), 3.42 (s, 3H), 6.85-7.0 (m, 2H), 7.1-7.7 (m, 32H).

5

EXAMPLE 30: N-[(2-((3'-N'-Propyl-(1''R)-3''α-(4-fluorophenyl)tropane-2''β-methoxymethylcarbamoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium (V) oxide

(Compound **22** (Re: R=4-F), FIG. 5) (O-1451)

10

N-[2-(3'-N'-propyl-(1''R)-3'' α-(4-fluorophenyl)tropane-2''β-(methoxymethylcarbamoyl))(2-((triphenylmethyl)thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol **21** (21 mg, 0.02 mmol) in EtOH (4 mL) was heated to reflux. A solution of SnCl₂ (8.4 mg, 0.04 mmol) in 0.005 M HCl (0.5 mL) was added quickly followed immediately by NaReO₄ (13 mg, 0.04 mmol) in 0.005 M HCl (0.5 mL). The solution was refluxed for 10h and was then loaded onto 0.5 g silica and pumped overnight. The silica-adsorbed material was applied to a chromatography column (3 g SiO₂, eluent 30% EtOAc/hexanes/5% Et₃N). Like fractions were combined and concentrated to yield as a purple foam (3.7 mg; 26%).

15

20 R_f 0.5 (25% hexanes in EtOAc); ¹H-NMR (CDCl₃) δ 1.1-4.2 (m, 30H), 4.5-4.6 (m, 1H), 4.75, 5.12 (2d, J=16.7Hz, 2x 6β, 1H), 6.8-7.0 (m, 2H), 7.1-7.2 (m, 2H).

EXAMPLE 31: 2 β -Methoxymethylcarbamoyl-3 β -(4-fluorophenyl)nortropane
(Compound **20A** (R=4-F), FIG. 5)

2 β -(1-Propanoyl)-3 β -(4-fluorophenyl)tropane (143 mg, 0.50 mmol) was combined with 1-chloroethyl chloroformate (2 mL) and the solution was heated to reflux for 2h. The excess chloroformate was removed in vacuo and the residue was refluxed in methanol (30 mL) for 45 min. The methanol was removed in vacuo and the residue was dissolved in CHCl₃ and NaHCO₃/Na₂CO₃ (pH=9). The aqueous layer was extracted CHCl₃ (3 x 10 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The residue was chromatographed (10-20% Et₃N in EtOAc). Like fractions were combined to yield 80 mg (58%).

¹H-NMR (CDCl₃) δ 1.50 (m, 1H), 1.7 (m, 2H), 1.95-2.22 (m, 2H), 2.5 (ddd, 1H), 2.92 (s, 3H), 3.1-3.4 (m, 2H), 3.3 (s, 3H), 3.6 (m, 1H), 3.72 (m, 1H), 6.9-7.0 (m, 2H), 7.1-7.3 (m, 2H).

EXAMPLE 32: N-[2-(3'-N'-Propyl-(1''R)-3'' β -(4-fluorophenyl)tropane-2'' β -methoxymethylcarbamoyl)((2-((triphenylmethyl)thio)ethyl)-amino)acetyl]-S-(triphenyl)-2-aminoethanethiol
(Compound **21A** (R=4-F), FIG. 5)

2 β -(1-Propanoyl)-3 β -(4-fluorophenyl)nortropane (80 mg, 0.28 mmol) was combined with MAMA'-Cl (244 mg, 0.32 mmol), KI (84 mg, 0.5 mmol, 2.0 eq.), and K₂CO₃ (322 mg, 2.3 mmol) in anhydrous MeCN (10 mL) and brought to reflux overnight then cooled to room temperature. The solvent was removed under vacuum

and the residue was applied to a chromatography column (5% Et₃N in EtOAc).

Fractions containing the product were combined and concentrated to yield the product as a light yellow foam (80 mg, 29%).

5 R_f 0.65 (5% Et₃N in EtOAc); ¹H-NMR (CDCl₃) δ 1.2-3.1 (m, 28H), 3.37 (m, 1H), 3.51 (s, 3H), 3.55 (m, 1H), 6.9-7.0 (m, 2H), 7.1-7.5 (m, 32H).

EXAMPLE 33: N-((2-((3'-N'-Propyl-(1''R)-3''β-(4-fluorophenyl)tropane-2''β-methoxymethylcarbamoyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium (V) oxide
10 (Compound **22A** (Re: R=4-F), FIG. 5) (O-1451)

N-[2-(3'-N'-propyl-(1''R)-3''β-(4-fluorophenyl)tropane-2''β-methoxymethylcarbamoyl)((2-((triphenylmethyl)thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (22 mg, 0.02 mmol) in EtOH (10 mL) was heated to reflux. A solution of
15 SnCl₂ (8.4 mg, 0.05 mmol) in 0.005 M HCl (1.0 mL) was added quickly followed immediately by NaReO₄ (13 mg, 0.05 mmol) in 0.005 M HCl (0.5 mL). The solution was refluxed for 10h and was then applied to a chromatography column (65% EtOAc/hexanes/5% Et₃N). Like fractions were combined and concentrated to yield a foam (10 mg; 65%).

20

R_f 0.44 (5% Et₃N, 30% hexanes in EtOAc); ¹H-NMR (CDCl₃) δ 1.5-4.2 (m, 30H), 4.4-4.6 (m, 1H), 4.72, 5.05 (2d, J=16.5Hz, 1H), 6.8-7.0 (m, 2H), 7.1-7.3 (m, 2H).

EXAMPLE 34: (1*R*)-*N*-Methyl-2-hydroxymethyl-3-(4-fluorophenyl)-8-aza-bicyclo[3.2.1]oct-2-ene (Compound **38** (R=4-F), FIG. 9) (O-1337)

(1*R*)-*N*-Methyl-2-methoxycarbonyl-3-(4-fluorophenyl)-8-azabicyclo[3.2.1]oct-2-ene **3** (500 mg, 1.82 mmol) was dissolved in benzene (15 mL) and LAH (70 mg, 1.82 mmol) was added. The reaction was heated to 60 °C overnight. The reaction was cooled to 0 °C, and water (70 µL), 15% NaOH (70 µL), water (200 µL) were added. The reaction was stirred for 15 min and then the salts were filtered off through a pad of celite. The filtrate was dried over Na₂SO₄ filtered and concentrated to yield **38** (454 mg, 90%) which was purified by column chromatography (30 g SiO₂; eluent: 4% Et₃N in 10% MeOH/CHCl₃). Like fractions were combined, reduced and pumped at high vacuum overnight to yield **38** (336 mg, 74%).

Mp. 106.6-108.7 °C; R_f 0.2 (10% MeOH/CHCl₃; 5% Et₃N); ¹H-NMR (CDCl₃) δ 1.5-1.7 (m, 1H), 1.9-2.0 (m, 3H), 2.1-2.3 (m, 2H), 2.4 (s, 3H), 2.72 (brd, J=18 Hz, 1H), 3.31 (br s, 1H), 3.55 (d, J=4.1 Hz, 1H), 3.89 (d, J=12.3 Hz, 1H), 4.02 (d, J=12.3 Hz, 1H), 6.9-7.0 (m, 2H), 7.1-7.2 (m, 2H). Elemental analysis: calculated C, 72.85, H, 7.34, N, 5.66; found C, 72.94, H, 7.33, N, 5.73.

EXAMPLE 35: (1*R*)-*N*-Methyl-2-hydroxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]oct-2-ene (Compound **38** (R=3,4-Cl₂), FIG. 9)

(1*R*)-*N*-Methyl-2-methoxycarbonyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]oct-2-ene **3** (508 mg, 1.56 mmol) was dissolved in benzene (20 mL) and LAH (62 mg, 1.56 mmol) was added. The reaction was heated to reflux overnight. The reaction was cooled to 0 °C, and water (80 µL), 10% KOH (90 µL), water (300 µL) were added.

The reaction was stirred for 15 min and then the salts were filtered off through a pad of celite. The filtrate was dried over Na₂SO₄ filtered and concentrated to yield a yellow foam (420 mg, 90%) and purified by column chromatography (3% Et₃N/ 7% MeOH in CHCl₃) to give 280 mg (60%).

5

R_f 0.2 (5% MeOH/CHCl₃; 3% Et₃N); ¹H-NMR (CDCl₃) δ 1.5-1.66 (m, 1H), 1.84-1.98 (m, 2H), 2.0 (m, 2H), 2.08-2.24 (m, 2H), 2.39 (s, 3H), 2.7 (dd, 1H), 3.3 (m, 1H), 3.54 (d, J=5.5Hz, 1H), 3.89 (d, J=11.8Hz, 1H), 4.01 (d, J=11.8Hz, 1H), 6.99 (dd, 1H), 7.25 (d, 1H), 7.37 (d, 1H).

10

EXAMPLE 36: (1*R*)-N-Methyl-2-carbonyl-3-(4-fluorophenyl)-8-azabicyclo[3.2.1]-oct-2-ene (compound **39** (R=4-F), FIG. 9)

A solution of (COCl)₂ (55 mg, 40 μL, 0.43 mmol) and CH₂Cl₂ (2 mL) was cooled to -78°C and DMSO (65 μL) was added dropwise over 3 min. The reaction was stirred for a further 5 min at -78°C and compound **38** (90 mg, 0.36 mmol) in CH₂Cl₂ (2 mL) was added dropwise over 10 min. After a further 20 min, Et₃N (250 μL, 1.80 mmol) was added over 30 min. The reaction was stirred for a further 10 min and then allowed to warm to room temperature. CH₂Cl₂ (20 mL) and 1M NaOH was added, the layers partitioned and the aqueous layer was washed with CH₂Cl₂ (1 x 15 mL).

20

Combined organic extracts were dried over Na₂SO₄, filtered, concentrated and pumped at high vacuum. The yellow oil obtained (86 mg) was purified by column chromatography (4.5g SiO₂; 30% EtOAc/hexanes/5% Et₃N) and like fractions were combined, concentrated and dried at high vacuum to yield the product **39** (62 mg,

63%).

R_f 0.2 (20% EtOAc/hexane, 5% Et₃N); ¹H-NMR (CDCl₃) δ 1.55-1.65 (m, 1H), 1.72-1.82 (m, 2H), 2.14-2.3 (m, 2H), 2.40 (s, 3H), 2.9-3.0 (m, 1H), 3.36-3.44 (m, 1H), 4.02-4.30 (m, 1H), 7.0-7.1 (m, 2H), 7.16-7.24 (m, 2H), 9.45 (s, 1H).

EXAMPLE 37: (1*R*)-N-Methyl-2-carbonyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]oct-2-ene (Compound **39** (R=3,4-Cl₂), FIG. 9)

A solution of (COCl)₂ (125 mg, 87 μL, 1.0 mmol) and CH₂Cl₂ (20 mL) was cooled to -78°C and DMSO (150 μL) was added dropwise over 3 min. The reaction was stirred for a further 5 min at -78°C and compound **38** (245 mg, 0.82 mmol) in CH₂Cl₂ (5 mL) was added dropwise over 7 min. After a further 30 min, Et₃N (600 μL, 4.0 mmol) was added over about 15 min. The reaction was stirred for a further 10 min. and then allowed to warm to room temperature. CH₂Cl₂ (20 mL) and Na₂CO₃ (20 mL; 1M) was added, the layers partitioned and the aqueous layer was washed with CH₂Cl₂ (1 x 20 mL). Combined organic extracts were dried Na₂SO₄, filtered, concentrated and pumped at high vacuum. The residue was purified by column chromatography (25g SiO₂; 60% EtOAc/hexanes/5% Et₃N) and like fractions were combined, concentrated and dried at high vacuum to yield the product **39** (154 mg, 63%).

R_f 0.2 (75% EtOAc/hexane, 5% Et₃N); ¹H-NMR (CDCl₃) δ 1.5-1.7 (m, 1H), 1.7-1.85 (m, 1H), 2.1-2.3 (m, 2H), 2.38 (s, 3H), 2.93 (dd, 1H), 3.39 (m, 1H), 4.05 (dd, 1H), 7.08

(dd, 1H), 7.34 (d, 1H), 7.46 (d, 1H), 9.45 (s, 1H).

EXAMPLE 38: (1*R*)-*N*-Methyl-2-(2-hydroxypropyl)-3-(4-fluorophenyl)-8-aza-bicyclo[3.2.1]oct-2-ene (Compound **40** (R=4-F), FIG. 9)

5 Compound **39** (62 mg, 0.26 mmol) was dissolved in anhydrous THF at room temperature and EtMgBr/Et₂O (3M; 900 μl) was added dropwise. The reaction was stirred at room temperature for 20 min and then at 65°C overnight, and then added slowly to a mixture of 1M HCl (50 mL) and Et₂O (50 mL) at 0°C. The mixture was basified with saturated aq. Na₂CO₃ and separated. The aqueous layer was extracted
10 with CHCl₃ (2 x 20 mL), dried (Na₂SO₄), filtered, evaporated and dried at high vacuum. The residue (90 mg) was purified by column chromatography (6 g SiO₂; 5% Et₃N/EtOAc) and like fractions were combined, evaporated and dried at high vacuum to yield **40** (82 mg, 52 %).

15 R_f 0.4 (10% MeOH/CHCl₃/5% Et₃N); ¹H-NMR (CDCl₃) δ 0.83 (t, J=7.6 Hz, 3H), 1.4-1.7 (m, 4H), 1.81 (d, J=18Hz, 1H), 2.0 (m, 1H), 2.1-2.3 (m, 2H), 2.42 (s, 3H), 2.7 (m, 1H), 3.3 (m, 1H), 3.53 (m, 1H), 4.1-4.2 (m, 1H), 6.9-7.1 (m, 4H)

20 EXAMPLE 39: (1*R*)-*N*-Methyl-2-(2-hydroxypropyl)-3-(3,4-dichlorophenyl)-8-aza-bicyclo[3.2.1]oct-2-ene (Compound **40** (R=3,4-Cl₂), FIG. 9)

Compound **39** (150 mg, 0.5 mmol) was dissolved in anhydrous THF (25 mL) at room temperature and EtMgBr/Et₂O (3M; 350 μl, 1.05 mmol) was added dropwise over 2 min. The reaction was stirred at room temperature for 2.75h and then added

slowly to a mixture of 1M HCl (20 mL) and Et₂O (20 mL). The mixture was basified with saturated aq. Na₂CO₃ and separated. The aqueous layer was extracted with CHCl₃ (3 x 20 mL) dried (Na₂SO₄), filtered, evaporated and dried at high vacuum.

The residue (197 mg) was purified by column chromatography (20 g SiO₂; 5%

Et₃N/EtOAc) and like fractions were combined, evaporated and dried at high vacuum to yield **40** (109 mg, 66%).

R_f 0.07 (5% Et₃N, 20% hexane in EtOAc); ¹H-NMR (CDCl₃) δ 0.85 (t, J=7.4 Hz, 3H), 1.4-1.7 (m, 4H), 1.79 (d, J=17.6 Hz, 1H), 1.95-2.1 (m, 1H), 2.1-2.3 (m, 2H), 2.42 (s, 3H), 2.68 (dd, J=4, 18 Hz, 1H), 3.3 (m, 1H), 3.38 (d, 1H), 3.52 (d, J=5 Hz, 1H), 4.1-4.2 (m, 1H), 6.94 (dd, 1H), 7.20 (dd, 1H).

EXAMPLE 40: (1*R*)-2-Propanoyl-3-(4-fluorophenyl)-8-azabicyclo[3.2.1]-oct-2-ene (Compound **26** (R=4-F), FIG. 9)

Tropane **40** (28 mg, 0.1 mmol) in CH₂Cl₂ was added dropwise to a cold (-78°C) solution of (COCl)₂ (5.5 μL, 0.12 mmol) and DMSO (20 μL, 0.26 mmol) in CH₂Cl₂.

After stirring for 30 min at -78°C, Et₃N (75 μL, 0.5 mmol) was added and the reaction was warmed to room temperature. CH₂Cl₂ and 1M NaOH were added and the layers separated. The organic layer was dried (Na₂SO₄), filtered and evaporated and the product applied to a chromatography column (5% Et₃N, 25% hexane, 70% EtOAc) to give 18.6 mg of product (66%).

R_f 0.2 (5% Et₃N, 25% Hexanes, 70% EtOAc); ¹H-NMR (CDCl₃) δ 0.80 (t, 3H), 1.6 (m,

1H), 1.8-2.3 (m, 6H), 2.40 (s, 3H), 2.75 (dd, 1H), 3.35 (m, 1H), 3.73 (m, 1H), 7.0 (m, 2H), 7.05-7.15 (m, 2H).

EXAMPLE 41: (1*R*)-2-Methoxycarbonyl-3-(4-fluorophenyl)-8-norazabicyclo[3.2.1]-
5 oct-2-ene (Compound **29** (R=4-F), FIG. 7) (O-1131)

2-Methoxycarbonyl-3-(4-fluorophenyl)tropene **3** (362 mg, 1.3 mmol) was combined with 1-chloroethyl chloroformate (1 mL) and the solution was heated to reflux for 2h. The excess chloroformate was removed in vacuo and the residue was refluxed in methanol (30 mL) for 45 min. The methanol was removed in vacuo and
10 the residue was dissolved in CHCl₃ and NaHCO₃/Na₂CO₃ (pH=9). The aqueous layer was extracted CHCl₃ (3 x 10 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The residue was chromatographed (eluent: 1-3% Et₃N in EtOAc + 0.5% NH₄OH). Like fractions were combined to yield a yellow solid (234 mg, 68%).

15 R_f 0.7 (10% MeOH in hexanes + 0.5% NH₄OH); mp. 67-68 °C; ¹H-NMR (CDCl₃) δ 1.50-3.0 (m, 6H), 3.8 (m, 1H), 4.2 (m, 1H), 6.8-7.2 (m, 4H). Elemental analysis: calculated C, 68.95, H, 6.17, N, 5.36; found C, 68.81, H, 6.24, N, 5.40.

20 EXAMPLE 42: (1*R*)-2-Methoxycarbonyl-3-(3,4-dichlorophenyl)-8-norazabicyclo[3.2.1]oct-2-ene (Compound **29** (R=3,4-Cl₂), FIG. 7) (O-1130)

2-Methoxycarbonyl-3-(3,4-dichlorophenyl)tropene (200 mg, 0.61 mmol) was combined with 1-chloroethyl chloroformate (4 mL) and the solution was heated to

reflux for 2h. The excess chloroformate was removed in vacuo and the residue was refluxed in methanol (30 mL) for 45 min. The methanol was removed in vacuo and the residue was dissolved in CHCl_3 and $\text{NaHCO}_3/\text{Na}_2\text{CO}_3$ (pH=9). The aqueous layer was extracted CHCl_3 (3 x 10 mL) and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The residue was chromatographed (eluent: 5-15% Et₃N in EtOAc). Like fractions were combined to yield a yellow oil.

R_f 0.3 (10% Et₃N in EtOAc); ¹H-NMR (CDCl₃) δ 1.50-2.3 (m, 5H), 2.5-2.9 (m, 1H), 3.53 (s, 3H), 3.8 (m, 1H), 4.2 (m, 1H), 6.9 (dd, 1H), 7.2 (dd, 1H), 7.4 (d, 1H). Elemental analysis: calculated C, 57.71, H, 4.84, N, 4.49; found C, 57.45, H, 4.87, N, 4.47.

EXAMPLE 43: N-[2-(3'-N'-Propyl-(1''R)-3''-(4-fluorophenyl)trop-2-ene-2''-(methoxycarbonyl))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (Compound **30** (R=4-F), FIG. 7)

2-(1-Methoxycarbonyl)-3-(4-fluorophenyl)nortrop-2-ene (134 mg, 0.5 mmol) was combined with MAMA'-Cl (387 mg, 0.5 mmol), KI (85 mg, 0.5 mmol), and K₂CO₃ (707 mg, 5 mmol) in anhydrous MeCN (10 mL) and brought to reflux overnight then cooled to room temperature. The solvent was removed under vacuum and the residue was applied to a chromatography column (1-6% Et₃N in EtOAc). Fractions containing the product were combined and concentrated to yield the product as a light yellow foam (148 mg, 29%).

R_f 0.18 (10% Et₃N in hexane); ¹H-NMR (CDCl₃) δ 1.3-3.15 (m, 22H), 3.2-3.4 (m, 1H),

3.5 (s, 3H), 3.8-3.9 (m, 1H), 6.8-7.8 (m, 34H).

EXAMPLE 44: N-[2-(3'-N'-Propyl-(1''R)-3''-(3,4-dichlorophenyl)trop-2-ene-2''-(methoxycarbonyl)((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (Compound **30** (R=3,4-Cl₂), FIG. 7)

2-(1-Methoxycarbonyl)-3-(3,4-dichlorophenyl)nortrop-2-ene (107 mg, 0.34 mmol) was combined with MAMA'-Cl (258 mg, 0.34 mmol), KI (57 mg, 0.34 mmol), and K₂CO₃ (472 mg, 3.4 mmol) in anhydrous MeCN (10 mL) and brought to reflux overnight then cooled to room temperature. The solvent was removed under vacuum and the residue was applied to a chromatography column (1-6% Et₃N in EtOAc). Fractions containing the product were combined and concentrated to yield the product as a foam (111 mg, 31%).

R_f 0.18 (5% Et₃N in hexane); ¹H-NMR (CDCl₃) δ 1.4-3.2 (m, 22H), 3.2-3.4 (m, 1H), 3.5 (s, 3H), 3.8-3.9 (m, 1H), 6.8-7.6 (m, 33H).

EXAMPLE 45: N-[(2-((3'-N'-Propyl-(1''R)-3''-(4-fluorophenyl)trop-2-ene-2''-methoxycarbonyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]rhenium (V) oxide (Compound **31** (Re: R=4-F), FIG. 7) (O-1135)

A solution of N-[2-(3'-N'-propyl-(1''R)-3''-(4-fluorophenyl)trop-2-ene-2''-(methoxycarbonyl)(2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (130 mg, 0.13 mmol) in EtOH (10 mL) was heated to reflux. A solution of SnCl₂ (28 mg, 0.15 mmol) in 0.005 M HCl (1.0 mL) was added quickly

followed immediately by NaReO₄ (40 mg, 0.15 mmol) in 0.005 M HCl (0.5 mL). The solution was refluxed for 10 h and was then applied to a chromatography column (1-10% Et₃N in EtOAc). Like fractions were combined and concentrated to yield a foam (34 mg; 37%).

R_f 0.09 (10% Et₃N in EtOAc); ¹H-NMR (CDCl₃) δ 1.4-4.3 (m, 23H), 3.5 (s, 3H), 4.5-4.9 (m, 2H), 6.9-7.2 (m, 4H). Elemental analysis: calculated C, 41.49, H, 4.50, N, 6.05; found C, 41.77, H, 4.44, N, 5.93. Accurate mass calculated 696.1348, found 696.1405.

EXAMPLE 46: N-[(2-((3'-N'-Propyl-(1''R)-3''-(3,4-dichlorophenyl)trop-2-ene-2''-methoxycarbonyl)(2-mercaptoethyl)amino)acetyl)-2-aminoethane-thiolato]rhenium (V) oxide (Compound **31** (Re: R=3,4-Cl₂), FIG. 7) (O-1136)

A solution of N-[2-(3'-N'-propyl-(1''R)-3''-(3,4-dichlorophenyl)trop-2-ene-2''-(methoxycarbonyl)(2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (100 mg, 0.1 mmol) in EtOH (10 mL) was heated to reflux. A solution of SnCl₂ (20 mg, 0.1 mmol) in 0.005 M HCl (1.0 mL) was added quickly followed immediately by NaReO₄ (29 mg, 0.11 mmol) in 0.005 M HCl (0.5 mL). The solution was refluxed for 10h and was then applied to a chromatography column (1-10% Et₃N in EtOAc). Like fractions were combined and concentrated to yield a foam (56 mg; 78%).

R_f 0.09 (10% Et₃N in EtOAc); ¹H-NMR (CDCl₃) δ 1.4-4.2 (m, 23H), 3.55 (s, 3H), 4.4-4.9 (m, 2H), 6.95 (dd, 1H), 7.2 (d, 1H), 7.4 (d, 1H). Elemental analysis: calculated C, 38.65, H, 4.05, N, 5.63; found C, 38.91, H, 3.96, N, 5.57. Accurate mass calculated 746.0663, found 746.0689.

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EXAMPLE 47: *N*-[2-(3'-*N*'-Propyl-(1''*R*-3''β-(4-fluorophenyl)-2''β-methoxycarbonyltropane))((2-((triphenylmethyl)thio)ethyl)amino)acetyl]-2-aminoethanethiol (Compound **33** (R=4-F), FIG. 8)

To a solution of nor-3β-(4-fluorophenyl)-2β-methoxycarbonyltropane (52.6 mg, 0.2 mmol) in dry acetonitrile (10 mL) was added in succession *N*-[2-((3-chloropropyl)-(2-((triphenylmethyl)thio)ethyl)amino)acetyl]-*S*-(triphenylmethyl)-2-aminoethanethiol (151 mg, 0.2 mmol), KI (33 mg, 0.2 mmol), and K₂CO₃ (280 mg, 2.0 mmol). The resulting slurry was then boiled overnight. Once the reaction was complete then the solution was allowed to cool to room temperature and then 2 g of silica gel was added and the solvent evaporated. The resulting solid was layered onto a silica gel column and eluted with 0.5% NH₄OH in 1:1 solution of EtOAc and hexanes. The title compound was recovered as a foam in 72 % yield (141 mg). This was converted to the dihydrochloride.

20 Mp. 166-168°C; IR (KBr) 1666 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.8-3.8, (m, 24H), 3.3 (s, 3H), 3.9-4.0 (m, 1H), 4.2-4.3 (m, 1H), 4.4-4.5 (m, 1H), 6.9-7.4 (m, 34 H). Elemental analysis: calculated (2 HCl • 2 H₂O): C, 68.24, H, 6.47, N, 3.85. Found: C, 38.03, H, 6.40, N, 3.82.

EXAMPLE 48: (RS)-N-[2-((3'-N'-Propyl-(1''R-3''β-(3,4-dichlorophenyl)-2''β-methoxycarbonyltropane))(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiol (Compound **33** (R=3,4-Cl₂), FIG. 8) (O-863)

Prepared identically to the compound in Example 47 above.

5

Mp. 108°C, IR (KBr) 1724, 1653, 957 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.5-3.9 (m, 22H), 3.55 & 3.50 (2s, 3H), 3.9-4.2 (m, 2H), 4.5-4.7 (m, 1H), 4.80 (d, 16.4 Hz, 1H), 7.0-7.4 (m, 3H); Accurate mass calculated for C₂₄H₃₃Cl₂N₃S₂O₄Re [MH]⁺ 748.0819, found 748.0856. Elemental analysis: calculated, C, 38.55, H, 4.31, N, 5.62. Found C, 38.79, H, 4.38, N, 5.41.

EXAMPLE 49: (RS)-N-[2-((3'-N'-Propyl-(1''R-3''β-(4-fluorophenyl)-2''β-methoxycarbonyltropane))(2-mercaptoethyl)amino)acetyl)-2-aminoethane thiolato]rhenium (V) oxide

(Compound **34** (Re: R=4-F), FIG. 8) (O-861)

N-[2-((3'-N'-Propyl-3''β-(4-fluorophenyl)tropane-2''β-carboxylic acid methyl ester)(2-((triphenylmethyl)thio)ethyl)amino)acetyl]-S-(triphenylmethyl)-2-aminoethanethiol (98 mg, 0.1 mmol) were dissolved in boiling ethanol (1.5 mL). To this was added a solution of SnCl₂ (21 mg, in 200 mL of 0.05 M HCl), followed immediately by a solution of NaReO₄ (30 mg in 200 mL of 0.05 M HCl). Boiling was continued overnight, after which boiling CH₃CN (10 mL) was added and the resulting solution filtered through a pad of celite. The cake was further washed two more times with boiling CH₃CN (2 x 20 mL). To the filtrate was added silica gel (1 g) and the

solvent evaporated. The solid was then layered onto a silica gel column and eluted with EtOAc. The title compound was isolated as a mixture of diastereomers in 90 % yield (608 mg).

5 Mp 101.9 °C, IR (KBr) 1720, 1666, 957 cm^{-1} ; ^1H -NMR (CDCl_3) δ 1.4-4.2, (m, 24H), 3.46 & 3.5 (2s, 3H), 4.4-4.7 (m, 1H), 4.80 & 4.82 (2d, 16 Hz, 1H), 6.8-7.3 (m, 4H); Accurate mass calculated for $\text{C}_{24}\text{H}_{34}\text{FN}_3\text{S}_2\text{O}_4\text{Re}$ $[\text{MH}]^+$ 698.1505, found 698.1557. This was converted to a hydrochloride for analysis: Elemental analysis: calculated ($\text{HCl} \cdot 2 \text{H}_2\text{O}$) C, 37.47, H, 4.98, N, 5.46. Found C, 37.45, H, 4.95, N, 5.40.

10
EXAMPLE 50: *(RS)*-N-[2-((3'-N'-Propyl-(1''R-3'' β -(3,4-dichlorophenyl)-2'' β -methoxycarbonyltropane))(2-mercaptoethyl)amino)acetyl)-2-aminoethane thiolato]rhenium (V) oxide
(Compound **34** (Re: R=3,4-Cl₂), FIG. 8) (O-863)

15 Prepared identically to the compound in Example 49 above.

Mp. 108°C, IR (KBr) 1724, 1653, 957 cm^{-1} ; ^1H -NMR (CDCl_3) δ 1.5-3.9 (m, 22H), 3.55 & 3.50 (2s, 3H), 3.9-4.2 (m, 2H), 4.5-4.7 (m, 1H), 4.80 (d, 16.4 Hz, 1H), 7.0-7.4 (m, 3H); Accurate mass calculated for $\text{C}_{24}\text{H}_{33}\text{Cl}_2\text{N}_3\text{S}_2\text{O}_4\text{Re}$ $[\text{MH}]^+$ 748.0819, found
20 748.0856. Elemental analysis: calculated, C, 38.55, H, 4.31, N, 5.62. Found C, 38.79, H, 4.38, N, 5.41.

EXAMPLE 51: (1*R*)-2β-Methoxycarbonyl-3α-(3,4-dichlorophenyl)-8-aza-bicyclo[3.2.1]octane (Compound **35** (R=3,4-Cl₂), FIG. 8)

(1*R*)-N-Methyl-2β-methoxycarbonyl-3α-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]-octane **12** (375 mg, 1.14 mmol) and α-chloroethyl chloroformate (ACE-Cl) (3 mL) were combined and heated at 100 °C (oil bath temperature) for 1h. Excess ACE-Cl was then removed under reduced pressure, and methanol (50 mL) was added to the residue. The mixture was then heated at reflux for 30 min and then concentrated to dryness. The residue obtained was dissolved in CH₂Cl₂ (75 mL), washed with aqueous NH₄OH, dried over Na₂SO₄, filtered, and concentrated to afford the crude demethylated product. Purification by flash chromatography (1% NH₄OH, 50-0% hexanes, 50-90% EtOAc 0-10% methanol) gave 250 mg (70%) of **35**.

R_f 0.14, (5% Et₃N/EtOAc/hexanes 1:1); ¹H-NMR (CDCl₃) δ 1.1-2.5 (m, 8H), 2.9-3.3 (m, 1H), 3.5-3.8 (m, 1H), 3.6 (s, 3H), 6.95-7.40 (m, 3H).

EXAMPLE 52: (1*R*)-2β-Methoxycarbonyl-3α-(4-fluorophenyl)-8-azabicyclo[3.2.1]-octane (Compound **35** (R=4-F), FIG. 8)

(1*R*)-N-Methyl-2β-methoxycarbonyl-3α-(4-fluorophenyl)-8-azabicyclo[3.2.1]-octane (95 mg, 0.34 mmol) and ACE-Cl (7 mL) were combined and heated at 100°C (oil bath temperature) for 1h. Excess ACE-Cl was then removed under reduced pressure, and methanol (50 mL) was added to the residue. The mixture was then heated at reflux for 30 min and then concentrated to dryness. The residue obtained was dissolved in CH₂Cl₂ (75 mL), washed with aqueous NH₄OH, dried over Na₂SO₄,

filtered, and concentrated to afford the crude demethylated product. Purification by flash chromatography (0-5% NH₄OH, 10% MeOH in EtOAc) gave 86 mg (95%) of **35**.

R_f 0.66, (10% MeOH/EtOAc + 0.5% NH₄OH); ¹H-NMR (CDCl₃) δ 1.2 (ddd, 1H), 1.2-2.8 (m, 5H), 3.3-3.6 (m, 2H), 3.5 (s, 3H), 3.8-4.2 (m, 2H), 6.9-7.3 (m, 4H).

EXAMPLE 53: N-[2-(3'-N'-Propyl-(1''R)-3''α-(3,4-dichlorophenyl)-2''β-methoxycarbonyltropane)]((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (Compound **36** (R=3,4-Cl₂), FIG. 8)

To a solution of (1R)-2β-methoxycarbonyl-3α-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane **35** (250 mg, 0.79 mmol) in dry CH₃CN (40 mL) was added in succession N-[[[2-[2-(triphenylmethyl) thio]ethyl](N'-3'-chloropropyl)amino]acetyl]-S-(triphenylmethyl)-2-aminoethanethiol (601 mg, 0.79 mmol), KI (132 mg), and K₂CO₃ (1.1 g). The resulting slurry was maintained at reflux overnight. Once the reaction was complete, the solution was allowed to cool to room temperature and then partitioned between concentrated aqueous NH₄OH and CH₂Cl₂. The layers were separated and the organic phase dried with Na₂SO₄. The solution was filtered and concentrated and the residue purified by flash chromatography (15 g, SiO₂; 0-5% Et₃N in a 1:1 mixture of EtOAc/hexanes) which gave 100 mg (12%) of a white foam.

R_f 0.26 (2.5% NH₄OH in EtOAc/hexanes 1/1); ¹H-NMR (CDCl₃) δ 1.20-1.54 (m, 5H), 1.80-2.50 (m, 15H), 2.81 (d, J=17Hz, 1H), 2.88 (d, J=17Hz, 1H), 3.00 (m, 2H), 3.16-3.40 (m, 3H), 3.54 (s, 3H), 7.03 (dd, J=2.2, 8.5Hz, 1H), 7.14-7.53 (m, 32H). Elemental

analysis: calculated, C, 72.07, H, 6.15, N, 4.07, Cl, 6.86; found C, 72.18, H, 6.21, N, 3.97, Cl, 6.75.

EXAMPLE 54: N-[2-(3'-N'-Propyl-(1''R)-3'' α -(4-fluorophenyl)-2'' β -methoxy-carbonyl-tropane))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (Compound **36** (R=4-F), FIG. 8)

To a solution of (1R)-2 β -methoxycarbonyl-3 α -(4-fluorophenyl)-8-azabicyclo [3.2.1]octane **35** (230 mg, 0.87 mmol) in dry CH₃CN (25 mL) was added in succession N-[[[2-[2-(triphenylmethyl) thio]ethyl](N'-3'-chloropropyl)amino]acetyl]-S-(triphenyl-methyl)-2-aminoethanethiol (660 mg, 0.87 mmol), KI (145 mg, 0.87 mmol), and K₂CO₃ (1.21 g, 8.7 mmol). The resulting slurry was then maintained at reflux overnight. Once the reaction was complete, the solution was allowed to cool to room temperature and then partitioned between concentrated aqueous NH₄OH and CH₂Cl₂. The layers were separated and the organic phase dried with Na₂SO₄. The solution was filtered and concentrated and the residue purified by flash chromatography (50% EtOAc/hexanes + 1% NH₄OH) which gave 435 mg (51%) of a foam.

R_f 0.45 (1% Et₃N, 50% EtOAc, 49% hexanes); ¹H-NMR (CDCl₃) δ 1.20 1.3 (m, 1H), 1.3-2.5 (m, 19H), 2.81 (d, J=17 Hz, 1H), 2.86 (d, J=17 Hz, 1H), 2.95-3.05 (m, 2H), 3.10-3.4 (m, 3H), 3.50 (s, 3H), 6.89-6.96 (m, 2H), 7.1-7.5 (m, 32H). Elemental analysis: calculated (0.75 H₂O), C, 74.78, H, 6.63, N, 4.22; found C, 74.80, H, 6.64, N, 4.17.

EXAMPLE 55: N-[(2-((3'-N'-Propyl-(1''R)-3'' α -(4-fluorophenyl)-2'' β -methoxy-carbonyltropane)(2-mercaptoethyl)amino)acetyl)-2-amino-ethanethiolato]-rhenium (V) oxide

(Compound **37** (R=4-F), FIG. 8) (O-1186)

A solution of N-[2-(3'-N'-propyl-(1''R)-3'' α -(4-fluorophenyl)-2'' β -methoxy-carbonyltropane)(2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethane-thiol (226 mg, 0.23 mmol) in EtOH (10 mL) was heated to reflux. A solution of SnCl₂ (48 mg, 0.25 mmol) in 0.05 M HCl (1.0 mL) was added quickly followed immediately by NaReO₄ (69 mg, 0.25 mmol) in 0.05 M HCl (0.5 mL). The solution was refluxed for 10 h and was then applied to a chromatography column (5% Et₃N in Et₂O). Like fractions were combined and concentrated to yield a foam (33 mg; 21%).

R_f 0.38 (10% Et₃N in EtOAc); ¹H-NMR (CDCl₃) δ 0.9-4.3 (m, 24H), 3.53, 3.56 (2s, 3H), 4.4-4.7 (m, 1H), 4.75, 5.00 (2s, 1H), 6.8-7.4 (m, 4H). Elemental analysis: calculated (2/7 Et₂O) C, 42.06, H, 5.03, N, 5.85; found C, 42.08, H, 4.93, N, 5.85.

EXAMPLE 56: N-[(2-((3'-N'-Propyl-(1''R)-3'' α -(3,4-dichlorophenyl)-2'' β -methoxy-carbonyltropane)(2-mercaptoethyl)amino)acetyl)-2-aminoethane-thiolato]rhenium (V) oxide (compound **37** (R=3,4-Cl₂), FIG. 8)

(O-1196)

Prepare identically to the compound in Example 55.

R_f 0.51 (10% Et₃N/EtOAc); ¹H-NMR (CDCl₃) δ 1.2-1.4 (m, 1H), 1.4-2.5 (m, 11H), 2.89 (m, 1H), 3.10-3.40 (m, 5H), 3.56 & 3.60 (2s, 3H), 3.6-3.8 (m, 0.5H), 3.90-4.15 (m, 3.5H), 4.60 (m, 1H), 4.73 & 4.95 (2d, J = 16.2 & 16.2Hz, 2 x 0.5H), 7.0-7.1 (m, 1H), 7.24-7.36 (m, 2H). Elemental analysis: calculated (H₂O), C, 37.64, H, 4.48, N, 5.49; found C, 37.59, H, 4.31, N, 5.55.

EXAMPLE 57: (1*R*)-N-Methyl-2-methoxycarbonyl-3-(2-naphthyl)-8-aza-bicyclo[3.2.1]oct-2-ene (Compound **50**, FIG. 10)

(1*R*)-2-(Methoxycarbonyl)-3-[[[(trifluoromethyl)sulfonyl]oxy] trop-2-ene **2** (500 mg, 1.52 mmol), LiCl (142 mg, 3.34 mmol), Pd₂dba₃ (56 mg, 0.06 mmol), Na₂CO₃ (2.0 M solution in water, 2 mL), diethoxymethane (6 mL) were all charged to a flask and stirred vigorously. To this solution was added 2-naphthyl boronic acid (340 mg, 1.97 mmol). The reaction was then brought to reflux for two hours and then filtered through celite. The cake was washed with ether and all the organic solution was washed with concentrated ammonium hydroxide solution. The washed solvent was dried with potassium carbonate, filtered, and evaporated. The residue was charged to a column (1-4% Et₃N/EtOAc) and gave 240 mg (51%) of compound **50**.

R_f 0.48 (10% Et₃N/EtOAc). ¹H-NMR (CDCl₃) δ 1.3-3.6 (m, 7H), 2.5 (s, 3H), 3.45 (s, 3H), 3.8-4.0 (m, 1H), 7.2-8.0 (m, 7H). Elemental analysis: calculated (0.5 H₂O) C, 77.24, H, 6.94, N, 4.50; found C, 77.27, H, 6.94, N, 4.48.

EXAMPLE 58: (1*R*)-2-Methoxycarbonyl-3-(2-naphthyl)-8-azabicyclo[3.2.1]-
oct-2-ene (Compound **51**, FIG. 10)

(1*R*)-*N*-Methyl-2-methoxycarbonyl-3-(2-naphthyl)-8-azabicyclo[3.2.1]-
oct-2-ene **50** (100 mg, 0.33 mmol) was combined with ACE-Cl (0.25 mL) and the
5 solution was heated to reflux for 5h. The excess chloroformate was removed in vacuo
and the residue was refluxed in methanol for 45 min. The methanol was removed in
vacuo and the residue was dissolved in CH₂Cl₂ and shaken with NaHCO₃/Na₂CO₃
(pH=9). The aqueous layer was extracted CH₂Cl₂ (4 x 10 mL) and the combined
organic extracts were dried (Na₂SO₄), filtered and concentrated. The residue was
10 chromatographed (1-10% Et₃N/EtOAc). Like fractions were combined to yield
compound **51** (27 mg, 28%).

R_f 0.15 (10% Et₃N/EtOAc); ¹H-NMR (CDCl₃) δ 1.6-2.5 (m, 5H), 2.7-3.1 (m, 1H), 3.45
(s, 3H), 3.8-3.9 (m, 1H), 4.2-4.35 (m, 1H), 7.1-8.0 (m, 7H).

EXAMPLE 59: N-[2-(3'-*N*'-Propyl-(1''*R*)-2''-methoxycarbonyl-3''-(2-naphthyl)-
trop-2-ene)](2-((triphenylmethyl) thio)ethyl)amino]acetyl]-S-
(triphenyl)-2-aminoethanethiol (Compound **52**, FIG. 10)

To a solution of (1*R*)-2-methoxycarbonyl-3-(2-naphthyl)-8-azabicyclo[3.2.1]-
20 oct-2-ene **51** (27 mg, 0.09 mmol) in dry CH₃CN (10 mL) was added in succession N-
[[[2-[2-(triphenylmethyl) thio]ethyl](*N*'-3'-chloropropyl)amino]acetyl]-S-(triphenyl-
methyl)-2-aminoethanethiol (70 mg), KI (15 mg), and K₂CO₃ (127 mg). The resulting
slurry was maintained at reflux overnight. Once the reaction was complete, the

solution was allowed to cool to room temperature and partitioned between conc. aq. NH₄OH and CH₂Cl₂. The layers were separated and the organic phase dried with Na₂SO₄. The solution was filtered and concentrated and the residue purified by flash chromatography (50-90% EtOAc/hexanes + 3% NH₄OH) which gave 27 mg (29%) of **52**.

R_f 0.44 (1% NH₄OH in EtOAc); ¹H-NMR (CDCl₃) δ 1.5-3.2 (m, 20H), 2.87 (s, 2H), 3.3-3.4 (m, 1H), 3.4 (s, 3H), 3.9-4.0 (m, 1H), 7.0-7.8 (m, 37H).

EXAMPLE 60: N-[(2-((3'-N'-Propyl-(1''R)-2''-methoxycarbonyl-3''-(2-naphthyl)trop-2-ene)(2-mercaptoethyl)amino)acetyl)-2-aminoethane-thiolato]-rhenium (V) oxide (Compound **41**, FIG. 10) (O-1185)

A solution of N-[2-(3'-N'-propyl-(1''R)-2''-methoxycarbonyl-3''-(2-naphthyl)trop-2-ene-))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethane-thiol **52** (27 mg, 0.027 mmol) in EtOH (10 mL) was heated to reflux. A solution of SnCl₂ (5.7 mg, 0.03 mmol) in 0.05 M HCl (1.0 mL) was added quickly followed immediately by NaReO₄ (8.2 mg, 0.03 mmol) in 0.05 M HCl (0.5 mL). The solution was refluxed for 10h and was then applied to a chromatography column (5% Et₃N in Et₂O). Like fractions were combined and concentrated to yield a mixture of the diastereomers (15 mg; 76%).

R_f 0.15 (10% Et₃N in EtOAc); IR (KBr) 967, cm⁻¹; Accurate mass calculated:

728.1599, found 728.1664; ¹H-NMR (CDCl₃) δ 1.3-4.3 (m, 23H), 3.45 (s, 3H), 4.5-4.9

(m, 2H), 7.1-8.0 (m, 7H).

EXAMPLE 61: (1*R*)-N-Methyl-2β-methoxycarbonyl-3β-(2-naphthyl)-8-aza-bicyclo[3.2.1]octane (Compound **42**, FIG. 10) (O-1229)

and

(1*R*)-N-Methyl-2β-methoxycarbonyl-3α-(2-naphthyl)-8-aza-bicyclo[3.2.1]octane (Compound **43**, FIG. 10) (O-1228)

To (1*R*)-N-Methyl-2β-methoxycarbonyl-3-(2-naphthyl)-8-azabicyclo[3.2.1]-oct-2-ene **50** (510 mg, 1.66 mmol) in THF (15 mL) at -78 °C was added SmI₂ solution (0.1 M in THF, 116 mL, 11.6 mmol) dropwise. After 30 min at -78°C MeOH (42 mL) was added and the resulting solution stirred at -78 °C for a further hour. The reaction was then quenched by adding TFA and water, the cold bath was also removed and the solution allowed to attain room temperature. The reaction was then made basic with NH₄OH and diluted with ether and then filtered through celite. The filter cake was washed with more ether and then all the organic phases were combined and washed with a sodium thiosulfate solution and then a brine solution. After drying with sodium sulfate the solution was filtered and concentrated and gave the crude products which were isolated by column chromatography (0-2% Et₃N in EtOAc). Compound **42** was isolated as a light yellow solid (110 mg, 22%).

Mp. 94-95 °C. R_f 0.28 (10% MeOH/CHCl₃); IR (KBr) 2900, 1750 cm⁻¹; ¹H-NMR (CDCl₃) δ 1.5-2.3 (m, 5H), 2.25 (s, 3H), 2.7 (ddd, 1H), 2.9-3.3 (m, 2H), 3.45 (s, 3H), 3.3-3.4 (m, 1H), 4.5-4.6 (m, 1H), 7.3-7.5 (m, 3H), 7.7-7.9 (m, 4H). Elemental analysis:

calculated (0.25 H₂O) C, 76.52, H, 7.55, N, 4.46; found C, 76.63, H, 7.57, N, 4.44.

Compound **43** was isolated as an off-white solid (113 mg, 23%).

5 M.p. 113-114 °C, R_f 0.56 (10% MeOH/CHCl₃); IR (KBr) 3000, 1750 cm⁻¹; ¹H NMR (CDCl₃) δ 1.4-1.6 (ddd, 1H), 1.4-1.8 (m, 3H), 2.0-2.4 (m, 2H), 2.3 (s, 3H), 2.4-2.7 (m, 1H), 2.65 (dd, 1H), 3.2-3.4 (m, 3H), 3.57 (s, 3H), 7.2-7.5 (m, 3H). Elemental analysis: calculated C, 77.64, H, 7.49, N, 4.53; found C, 77.48, H, 7.50, N, 4.45.

10 EXAMPLE 62: (1*R*)-2β-Methoxycarbonyl-3β-(2-naphthyl)-8-azabicyclo[3.2.1]-octane (Compound **44**, FIG. 10)

(1*R*)-N-Methyl-2β-methoxycarbonyl-3β-(2-naphthyl)-8-azabicyclo[3.2.1]octane **42** (146 mg) was combined with ACE-Cl (5.5 mL) and the solution was heated to reflux for 5h. The excess chloroformate was removed in vacuo and the residue was refluxed in methanol for 45 min. The methanol was removed in vacuo and the residue was dissolved in CH₂Cl₂ and shaken with NaHCO₃/Na₂CO₃ (pH=9). The aqueous layer was extracted CH₂Cl₂ and the combined organic extracts were dried (Na₂SO₄), filtered and concentrated. The residue was chromatographed (2% MeOH/EtOAc). Like fractions were combined to yield **44** (109 mg, 78%).

20 R_f 0.27 (10% MeOH/EtOAc); ¹H-NMR (CDCl₃) δ 1.5-2.4 (m, 5H), 2.68 (ddd, 1H), 4.8-4.9 (m, 1H), 3.30 (s, 3H), 3.3-3.4 (m, 1H), 3.7-3.9 (m, 2H), 7.1-8.0 (m, 7H). Elemental analysis: calculated (0.25 H₂O) C, 76.10, H, 7.23, N, 4.67; found C, 75.98, H, 7.23, N,

4.60.

EXAMPLE 63: (1*R*)-2β-Methoxycarbonyl-3 α-(2-naphthyl)-8-azabicyclo[3.2.1]-
octane (Compound **45**, FIG. 10)

5 (1*R*)-N-Methyl-2β-methoxycarbonyl-3α-(2-naphthyl)-8-azabicyclo[3.2.1]-
octane, **43** (90 mg, 0.29 mmol) was combined with ACE-Cl (4 mL) and the solution
was heated to reflux for 5h. The excess chloroformate was removed in vacuo and the
residue was refluxed in methanol for 45 min. The methanol was removed in vacuo
and the residue was dissolved in CH₂Cl and shaken with NaHCO₃/Na₂CO₃ (pH=9).
10 The aqueous layer was extracted CH₂Cl and the combined organic extracts were dried
(Na₂SO₄), filtered and concentrated. The residue was chromatographed (2%
MeOH/CHCl₃). Like fractions were combined to yield **45** (109 mg, 78%).

R_f 0.29 (10% MeOH/CHCl₃).

15 EXAMPLE 64: N-[2-(3'-N'-Propyl-(1''*R*)-2''β-methoxycarbonyl-3''β-(2-naphthyl)-
tropane)]((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-
(triphenyl)-2-aminoethanethiol (Compound **46**, FIG. 10)

To a solution of (1*R*)-2β-methoxycarbonyl-3β-(2-naphthyl)-8-aza-
20 bicyclo[3.2.1]octane **44** (81 mg, 0.27 mmol) in dry CH₃CN (20 mL) was added in
succession N-[[[2-[2-(triphenylmethyl)thio]ethyl](N'-3'-chloropropyl)amino]acetyl]-S-
(triphenylmethyl)-2-aminoethanethiol (207 mg), KI (46 mg, 0.27 mmol), and K₂CO₃
(378 mg). The resulting slurry was then maintained at reflux overnight. Once the

reaction was complete, the solution was allowed to cool to room temperature and then partitioned between concentrated aqueous NH_4OH and CH_2Cl_2 . The layers were separated and the organic phase dried with Na_2SO_4 . The solution was filtered and concentrated and the residue purified by flash chromatography (0-90%

5 EtOAc/hexanes + 3% NH_4OH) which gave 150 mg (54%) of **46**.

R_f 0.36 (10% Et_3N in EtOAc); $^1\text{H-NMR}$ (CDCl_3) δ 1.4-3.8 (m, 24H), 2.85 (s, 2H), 3.38 (s, 3H), 7.0-7.8 (m, 37H).

10 EXAMPLE 65: N-[2-(3'-N'-Propyl-(1''R)-2'' β -methoxycarbonyl-3'' α -(2-naphthyl)-tropane))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-aminoethanethiol (Compound **47**, FIG. 10)

To a solution of (1R)-2 β -methoxycarbonyl-3 α -(2-naphthyl)-8-azabicyclo[3.2.1]octane **45** (17 mg, 0.06 mmol) in dry CH_3CN (10 mL) was added in succession N-[[[2-[2-(triphenylmethyl)thio]ethyl](N'-3'-chloropropyl)amino]acetyl]-S-(triphenylmethyl)-2-aminoethanethiol (4.3 mg), KI (9.4 mg), and K_2CO_3 (79 mg). The resulting slurry was then maintained at reflux overnight. Once the reaction was complete, the solution was allowed to cool to room temperature and then partitioned between concentrated aqueous NH_4OH and CH_2Cl_2 . The layers were separated and the organic phase dried with Na_2SO_4 . The solution was filtered and concentrated and the residue purified by flash chromatography (50-80% EtOAc/hexanes + 3% NH_4OH) which gave 18 mg (31%) of **47**.

R_f 0.16 (50% EtOAc), 47% hexane, 3% NH₄OH).

EXAMPLE 66: N-[(2-((3'-N'-Propyl-(1''R)-2''β-methoxycarbonyl-3''β-(2-naphthyl)-
tropane)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-
rhenium (V) oxide (Compound **48**, FIG. 10) (O-1339)

A solution of N-[2-(3'-N'-propyl-(1''R)-2''β-methoxycarbonyl-3''-(2-naphthyl)-
trop-2-ene))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-amino-
ethanethiol **46** (150 mg, 0.15 mmol) in EtOH (10 mL) was heated to reflux. A solution
of SnCl₂ (31 mg, 0.16 mmol) in 0.05 M HCl (1.0 mL) was added quickly followed
immediately by NaReO₄ (45 mg, 0.16 mmol) in 0.05 M HCl (0.5 mL). The solution
was refluxed for 10h and was then applied to a chromatography column (5% Et₃N in
EtOAc). Like fractions were combined and concentrated to yield a mixture of the
diastereomers (34 mg; 41%).

R_f 0.39 (10% Et₃N in EtOAc); ¹H-NMR (CDCl₃) δ 1.4-4.2 (m, 24H), 3.40, 3.48 (2s, 3H),
4.4-4.7 (m, 1H), 8.25, 8.30 (2d, 1H), 7.2-8.0 (m, 7H). Elemental analysis: calculated
(0.5 EtOAc) C, 46.97, H, 5.30, N, 5.39; found C, 46.91, H, 5.12, N, 5.19.

EXAMPLE 67: N-[(2-((3'-N'-Propyl-(1''R)-2''β-methoxycarbonyl-3''α-(2-naphthyl)-
tropane)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-
rhenium (V) oxide (Compound **49**, FIG. 10)

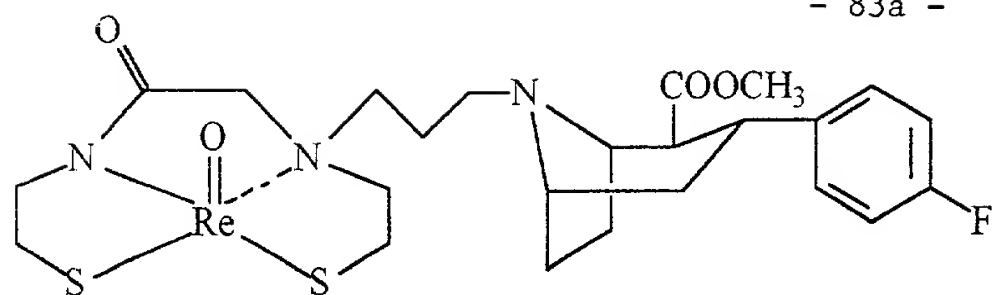
A solution of N-[2-(3'-N'-propyl-(1''R)-2''β-methoxycarbonyl-3''α-(2-
naphthyl)-trop-2-ene))((2-((triphenylmethyl) thio)ethyl)amino)acetyl]-S-(triphenyl)-2-

amino-ethanethiol **47** (18 mg, 0.02 mmol) in EtOH (10 mL) was heated to reflux. A solution of SnCl₂ (5.3 mg) in 0.05 M HCl (1.0 mL) was added quickly followed immediately by NaReO₄ (3.7 mg) in 0.05 M HCl (0.5 mL). The solution was refluxed for 10h and was then applied to a chromatography column (5% Et₃N in Et₂O). Like
5 fractions were combined and concentrated to yield a mixture of the diastereomers (40%).

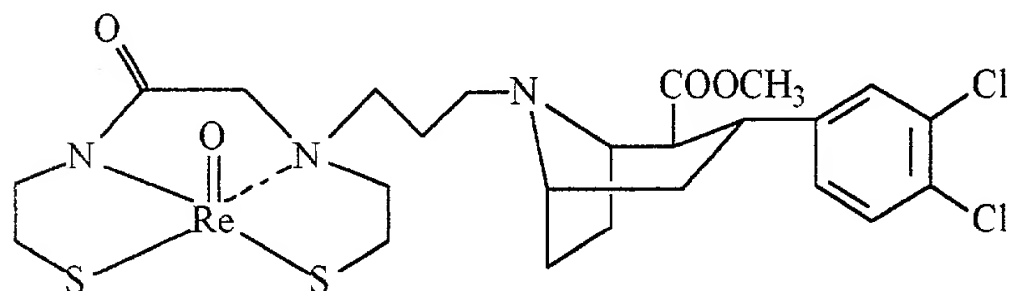
R_f 0.46 (5% Et₃N in EtOAc); ¹H-NMR (CDCl₃) δ 1.4-1.8 (m, 24H), 1.8-2.0 (m, 2H),
2.02-2.20 (m, 1H), 2.3-2.5 (m, 3H), 2.69, 2.71 (2s, 3H), 2.9-3.0 (2dd, 1H), 3.1-3.4 (m,
10 3H), 3.4-3.6 (m, 1H), 3.5,3.55 (2s, 3H), 3.6-3.8 (2ddd, 1H), 3.9-4.2 (m, 3H), 4.5-4.7 (m,
1H), 4.75, 4.98 (2d, 1H), 7.32 (d, 1H), 7.3-7.5 (m, 2H), 7.64 (s, 1H), 7.7-7.8 (m, 3H).

EXAMPLES 68 - 80

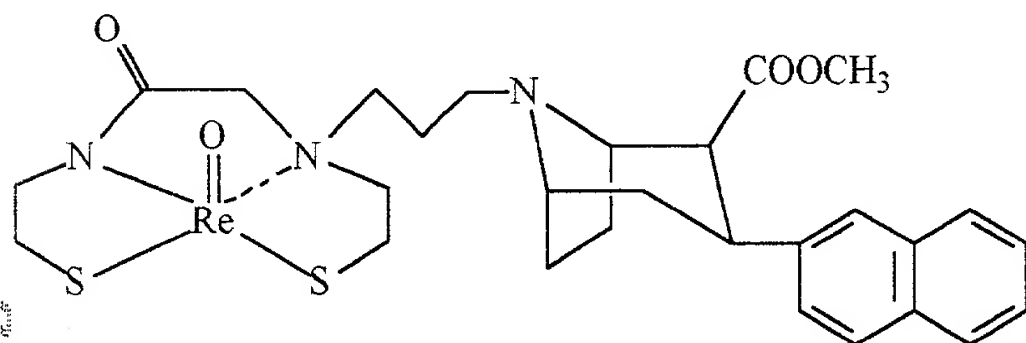
Tests were conducted to determine the binding affinity and selectivity of
15 certain compounds for the dopamine transporter. The results are tabulated below.



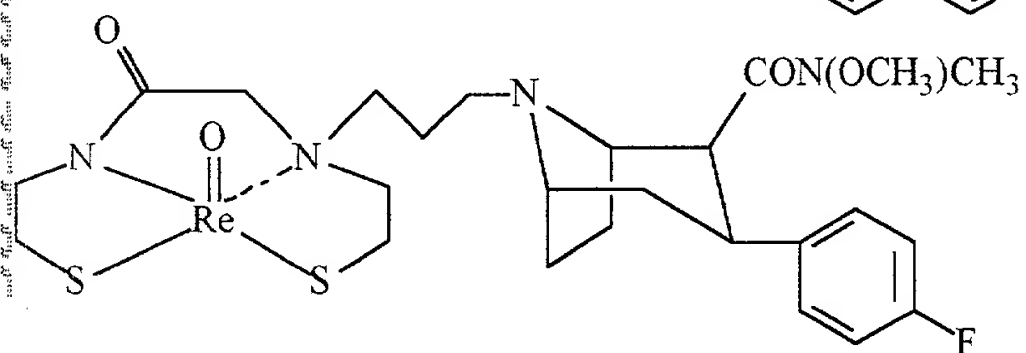
O-1186



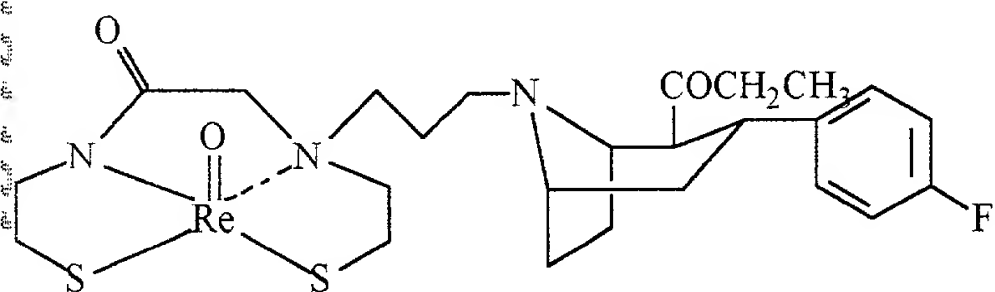
O-1196



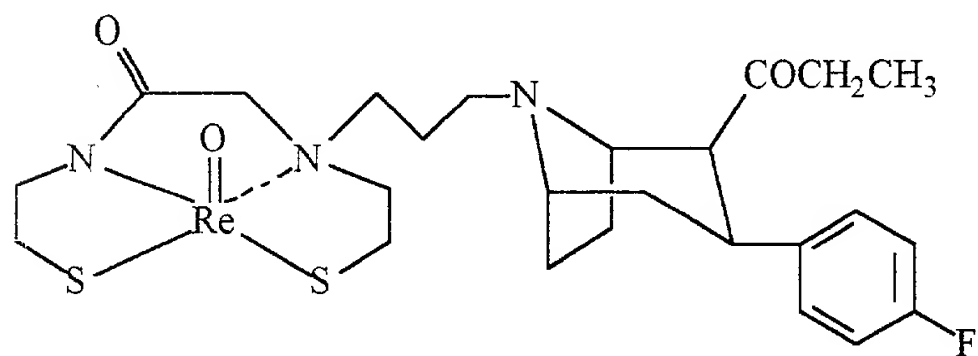
O-1339



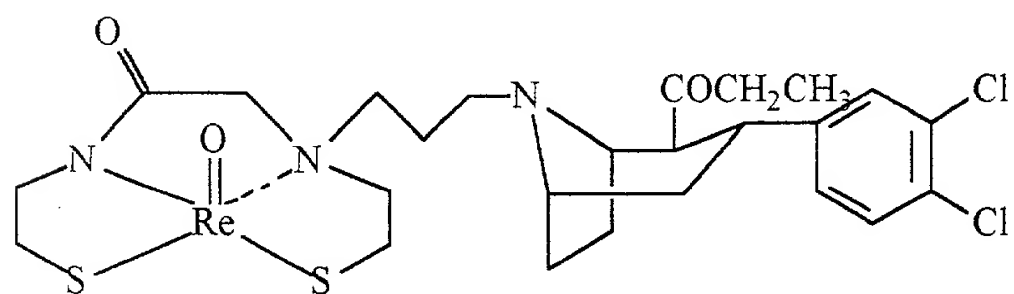
O-1451



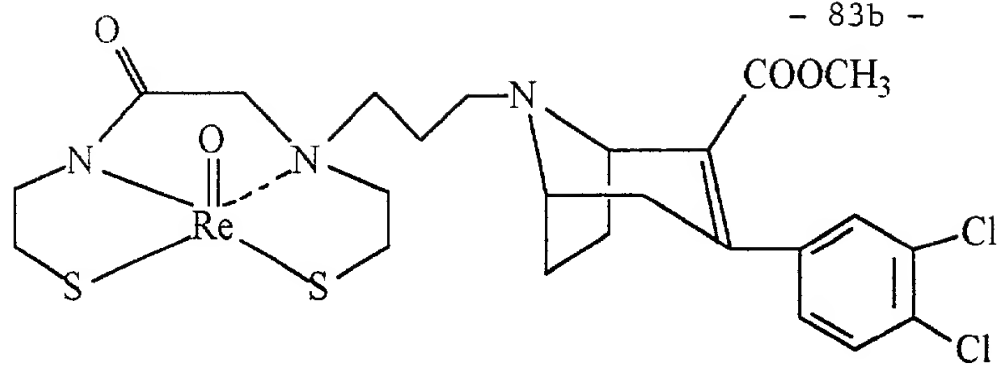
O-1505



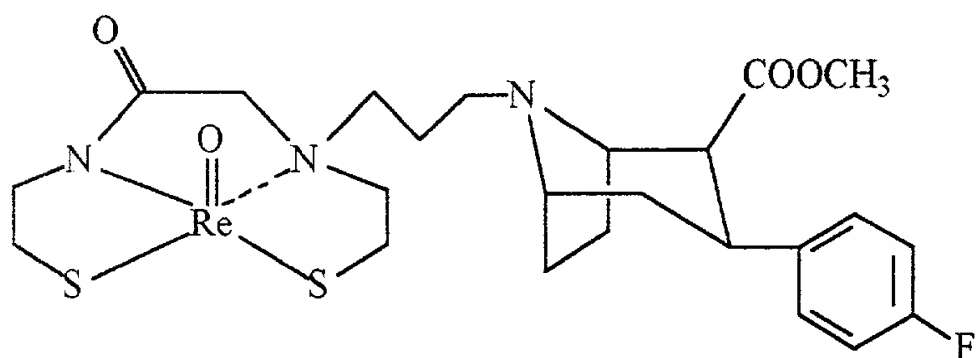
O-1508



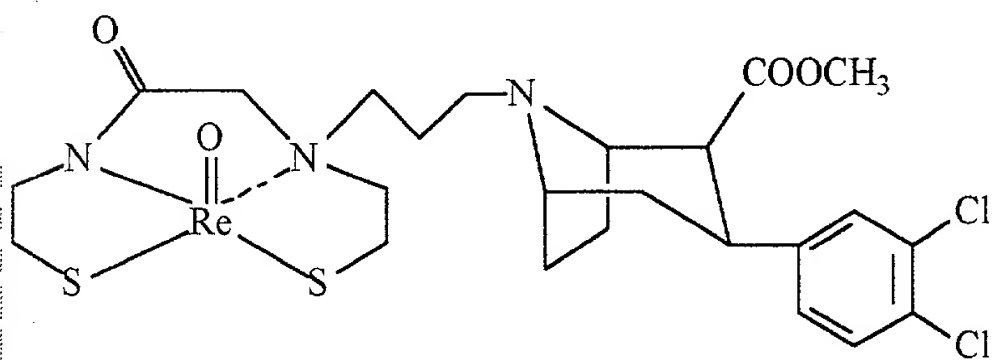
O-1561



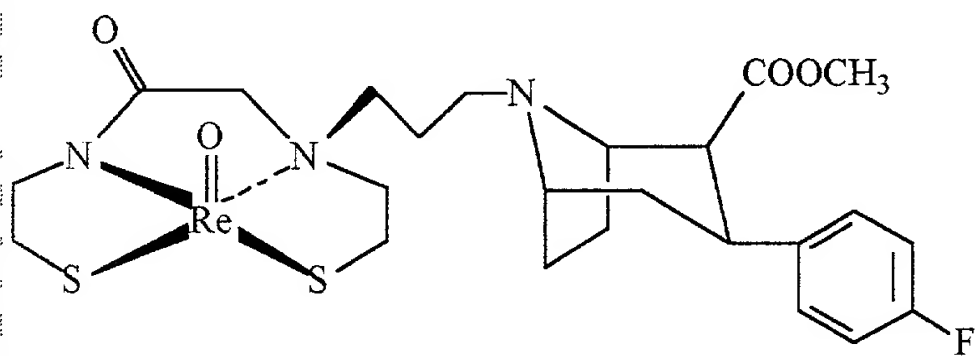
O-1136



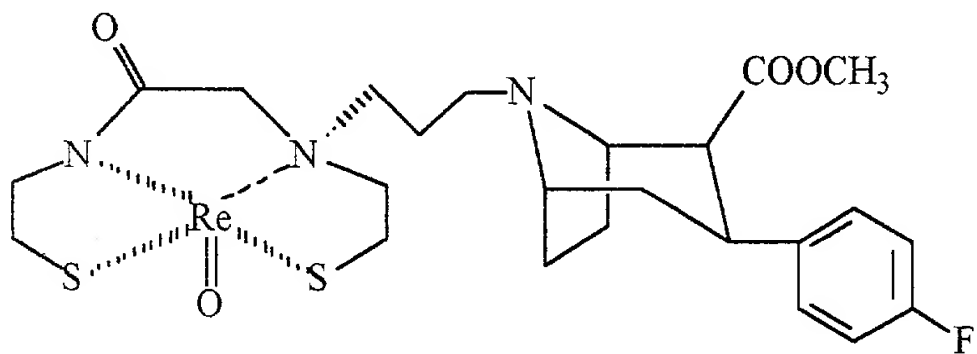
O-861



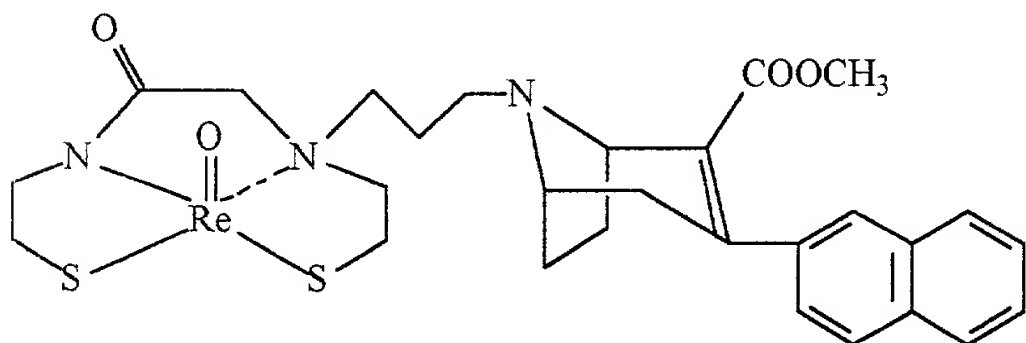
O-863



O-927



O-928



O-1185

	Example	Compound	IC50 DAT	IC50 SERT	DAT/ SERT
	68	O-1136	60	1693	28
	69	O-861	2.9	80	28
5	70	O-863	40	-	-
	71	O-927	5.0	200	40
	72	O-928	3.0	30	10
	73	O-1185	63	960	15
	74	O-1186	3.8	1300	340
10	75	O-1196	10	640	64
	76	O-1339	3.6	59	16
	77	O-1451	40	3260	80
	78	O-1505	2.0	497	249
	79	O-1508	5.9	200	34
15	80	O-1561	5.3	337	63

EXAMPLES 81 - 91: ^{99m}Tc Labeling

The following compounds were prepared by identical methods described below.

20 81 N-[(2-((3'-N'-Propyl-(1''R)-2''β-methoxycarbonyl-3''α-(3,4-dichlorophenyl)-tropane)-(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-technetium (V) oxide (Compound **37** (R=3,4-Cl₂), FIG. 8) (O-1196)

82 N-[(2-((3'-N'-Propyl-(1''R)-2''β-1-propanoyl-3''α-(4-fluorophenyl)-tropane)-
(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]technetium (V) oxide
(Compound **19** (R=4-F), FIG. 4)

5 83 N-[(2-((3'-N'-Propyl-(1''R)-2''β-1-propanoyl-3''α-(3,4-dichlorophenyl)-
tropane)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-
technetium (V) oxide (Compound **19** (R=3,4-Cl₂), FIG. 4)

10 84 N-[(2-((3'-N'-Propyl-(1''R)-2''β-methoxymethylcarbamoyl-3''α-(4-
fluorophenyl)-tropane)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-
technetium (V) oxide (Compound **22** (R=4-F), FIG. 5) (O-1451)

15 85 (RS)-N-[2-((3'-N'-Propyl-(1''R)-2''β-carbomethoxy-3''β-(4-fluorophenyl)-
tropane))(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-
technetium (V) oxide (Compound **34** (R=4-F), FIG. 8)

86 (RS)-N-[2-((3'-N'-Propyl-(1''R)-2''β-carbomethoxy-3''β-(3,4-dichlorophenyl)-
tropane))(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-technetium (V)
oxide (Compound **34** (R=3,4-Cl₂), FIG. 8)

20 87 N-[(2-((3'-N'-Propyl-(1''R)-2''-carbomethoxy-3''-(4-fluorophenyl)-
tropene)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-
technetium (V) oxide (Compound **31** (R=4-F), FIG. 7)

88 N-[(2-((3'-N'-Propyl-(1''R)-2''-methoxycarbonyl-3''-(3,4-dichlorophenyl)-
tropene)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-
technetium (V) oxide (Compound **31** (R=3,4-Cl₂), FIG. 7)

5 89 N-[(2-((3'-N'-Propyl-(1''R)-2''β-methoxycarbonyl-3''α-(4-fluorophenyl)-
tropane)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-
technetium (V) oxide (Compound **37** (R=4-F), FIG. 8)

10 90 N-[(2-((3'-N'-Propyl-(1''R)-3''β-(4-fluorophenyl)tropane-2''β-1-propanoyl)-
(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]technetium (V) oxide
(Compound **11** (R=4-F), FIG. 3)

15 91 N-[(2-((3'-N'-Propyl-(1''R)-2''β-1-propanoyl-3''β-(3,4-dichlorophenyl)-
tropane)(2-mercaptoethyl)amino)acetyl)-2-aminoethanethiolato]-technetium (V)
oxide (Compound **11** (R=3,4-Cl₂), FIG. 3)

Deprotection of tropane analog for radiolabeling:

The following is a description of the procedures that were employed:

20 Twenty microliter aliquots of TFA, CH₂Cl₂, and (C₂H₅)₃SiH were added to 5.0
mg of each trityl protected precursor to cleave the thiol protecting group. After a 20
min. incubation, 200μL of 1.0 M HCl / Ether was added to protonate the thiols. The
solvent was evaporated off, followed by successive washes with hexanes to remove the
trityl groups. The deprotected compound was then dissolved in DMSO to produce a
stock solution at a concentration of 1 mg/mL.

Radiolabeling the tropane analog:

Approximately 200 mCi of sodium ^{99m}Tc pertechnetate was added to a Glucoheptonate kit (Du Pont Pharmaceuticals, Billerica, MA) and allowed to incubate at room temperature for 15 min. 150 mCi of the resulting ^{99m}Tc -Glucoheptonate was added to an equal volume of 50 mM Acetate Buffer, pH 5.2 (approximately 2 mL) and 50 μL of deprotected precursor stock solution (1 mg/mL in DMSO, 50 μg). This solution was incubated at room temperature for 20 min. The course of the radiolabeling was monitored with a Rainin HPLC system using a reverse phase Vydac C8 column (4.6 x 250 mm 5 μm). The column was eluted with a 0.1M ammonium acetate/acetonitrile mobile phase; 1.5 mL/min. flow rate, and a gradient of 5-100% acetonitrile over 15 minutes. Radioactive detection is achieved with a Frisk - Tech Rate meter (Bicron Corp.). The final radiolabeled product was purified using a C18 Sep-Pak (Waters Inc.) eluted with ethanol. For all compounds, labeling yields and radiochemical purities were greater than 85 % and 98 %, respectively. Each product was diluted with sterile saline to yield a <10% ethanol solution followed by filtration through a 0.22 μm filter prior to injection. Typical HPLC chromatograms are shown in Figures 11 - 14.

Summary of analytical results, HPLC:

With the above methodology, it was observed that the retention times were dependent upon two features of the analog, i.e., the conformation and the substituents. As expected the dichloro-analogs eluted later than the monofluorinated compounds and the boat conformers eluted later than the respective chair

compounds. Retention times for four specific ^{99m}Tc labeled compounds are tabulated below. The reproducibility was ± 0.1 min.

Example No.	Compound	Retention Time(min.)
Example 82	0-1505T	16.6
Example 90	0-1508T	15.2
Example 83	0-1561T	17.1
Example 91	0-1506T	16.1

Animal model of Parkinson's disease:

The neurotoxin MPTP (N-methyl-1,2,3,6-tetrahydropyridine), when administered to monkeys, produces a spectrum of motor, cognitive, biochemical and morphological changes that is not replicated in rodents. MPTP-treated monkeys develop neurological deficits (resting tremor, rigidity, akinesia, postural abnormalities), morphological changes (cell loss in the substantia nigra, ventral tegmental area, retrorubal fields) and biochemical changes (severe depletion of DA and decreases in norepinephrine and serotonin) that closely, parallel idiopathic PD and post-encephalitic Parkinsonism.

Two monkeys were treated with MPTP; 3-5 doses of 0.6 mg/kg administered over 10 days. Treatment was performed under ketamine anesthesia (15 mg/kg). This dose of MPTP, has previously been used to produce Parkinsonism within 2-3 weeks

and depletion of ^3H or ^{11}C CFT binding sites by one month. Animals treated in this manner were expected to show an inverse relationship between SPECT tracer binding and motor dysfunction. The marked depletion of DA terminals produced by this treatment should provide definitive evidence of the selectivity and sensitivity of the SPECT tracers to detect full depletion of the nerve terminals.

SPECT imaging

All SPECT images were acquired with a MultiSPECT 2 gamma camera (Siemens, Hoffman Estates, IL) equipped with fan-beam collimators and peaked to the 140 KeV photopeak of $^{99\text{m}}\text{Tc}$ (15% window). This camera has intrinsic resolution of 4.6 mm (FWHM), and a sensitivity of ~ 240 cps/mCi. Images were acquired over 360° (60 projections / head, 128×128 matrix) in the continuous mode. Image reconstruction was performed using a conventional filtered back-projection algorithm to an in-plane resolution of 10 mm FWHM and attenuation correction via the Chang method.

Rhesus monkeys weighing approximately 7 kg were anesthetized with ketamine/xylazine (15.0 and 1.5 mg/kg) and positioned prone on the imaging bed of the SPECT camera. Before the start of imaging, a venous catheter was inserted in a peripheral vein for radiopharmaceutical administration. The heads of the animals were immobilized with a custom fabricated head holder. Approximately 20-25 mCi of $^{99\text{m}}\text{Tc}$ labeled O-1505T, O-1508T, O-1561T or O-1560T was injected intravenously over 60 seconds. Dynamic SPECT imaging was initiated at the end of the infusion and consisted of 2 min. acquisitions during the first hour and 5 min. acquisitions

thereafter.

Selectivity of For DAT Sites in the Monkey Brain

For this study, a monkey was positioned supine on the imaging table of the
5 MultiSPECT 2 gamma camera and injected with ~20 mCi of ^{99m}Tc O-1560T as
described above. At approximately 20 min. after radiopharmaceutical administration,
the animal was injected with CFT (1.0 mg/kg) and imaging was continued for an
additional 70 min.

10 *Image analysis*

SPECT slices with greatest striatal activity or in which the occipital cortex was
well visualized were summed and regions of interest (ROI's) were constructed. In the
striatal planes, ROI's were placed on the right and left striatum (caudate + putamen).
Radioactivity in the right and left striatum were averaged. ROI radioactivities
15 (cpm/cc) were decay corrected to the time of injection. The difference between striatal
and occipital cortex activity (specific binding) was calculated for each image and was
plotted as a function of time. Corrections for scattered fraction and partial volume
effects were not performed.

20 *Radiation dosimetry*

Groups of male Sprague-Dawley rats were injected with ~10 mCi of ^{99m}Tc
labeled O-1505T and O-1561T. At time intervals between 5 min. and 24 hrs after
injection, groups of 6 animals injected with each radiopharmaceutical were sacrificed
and biodistribution was measured. Samples of blood, heart, lung, liver, spleen,

kidney, adrenal, stomach, GI tract, testes, bone, bone marrow and skeletal muscle were weighed and radioactivity was measured with a well type gamma counter (LKB model # 1282, Wallac Oy, Finland). To correct for radioactive decay and permit calculation of the concentration of radioactivity in each organ as a fraction of the administered dose, aliquots of the injected doses were counted simultaneously. The results were expressed as percent injected dose per gram (%I.D./g) and radiation dosimetry was estimated by the MIRdose method.

RESULTS

SPECT imaging with ^{99m}Tc labeled O-1505T, O-1508T, O-1561T and O-1560T

In the images acquired early after injection of ^{99m}Tc O-1505T and ^{99m}Tc O-1561T, diffuse accumulation of radioactivity was observed throughout the brain. Over the first several minutes after injection, accumulation of tracer in the striatum intensified and the level of radioactivity in all other structures decreased. By 30 minutes after injection there was excellent contrast between striatum and the rest of the brain. Trans-axial, sagittal and coronal images of monkey brains were acquired between 30 and 50 minutes after injection of ^{99m}Tc labeled O-1505T, O-1508T, O-1561T and O-1560T. From these data, it is clear that the images acquired after injection of ^{99m}Tc O-1505T and ^{99m}Tc O-1561T (boat forms of the monofluoro and dichloro compounds, respectively) display high concentrations of radiopharmaceutical in the striatum with minimal accumulation in other areas of the brain. In particular, lack of accumulation in the thalamus, hypothalamus or midbrain, regions that are rich in 5-HT transporters, supports the specificity of this tracer for DAT sites. Region of interest analysis yielded striatal to occipital cortex ratios of approximately ~2.5 to 1.

In this experiment, images acquired after injection of ^{99m}Tc O-1508T and ^{99m}Tc O-1560T (chair forms of the monofluoro and dichloro compounds, respectively) differed with O-1508T failing to demonstrate significant accumulation of radioactivity in striatum or elsewhere in the brain while O-1560T provided results more like O-1505T and O-1561T.

SPECT of MPTP treated monkeys

(Mid-striatal) trans-axial, sagittal and coronal SPECT images of the brain of a rhesus monkey injected with ^{99m}Tc O-1505T were obtained one month after MPTP treatment. Compared with normal animals, after MPTP treatment, the level of accumulation decreased markedly and the striatum could not be differentiated from surrounding structures.

Selectivity of ^{99m}Tc O-1505T for DAT sites in monkey brain

SPECT images of monkey brain showed significant accumulation of ^{99m}Tc O-1505T in the striatum. In the early images there was diffuse accumulation of radioactivity throughout the brain. Over the first several minutes after injection, accumulation of tracer in the striatum intensified and the level of radioactivity in all other structures decreased. By 30 minutes after injection there was excellent contrast between striatum and the rest of the brain. After injection of a receptor saturating dose of unlabeled CFT, striatal accumulation of radioactivity decreased and by 60 minutes after injection, there was no evidence of focal accumulation in the striatum.

Radiation dosimetry

The biodistribution studies demonstrated that both ^{99m}Tc O-1505T and ^{99m}Tc O-1561 cleared rapidly from all tissues of the rat. For ^{99m}Tc O-1505T, MIRdose calculations revealed urinary bladder to be the target organ with a dose of 0.29
5 rem/mCi. Total body effective dose was estimated at 0.037 rem/mCi

Summary:

These results demonstrate that ^{99m}Tc labeled O-1505T and O-1561T are excellent SPECT ligands for DAT sites. These radiopharmaceuticals combine the the
10 following important characteristics for obtaining useful diagnostic images: (1) high striatal to occipital cortex ratios; (2) high selectivity for DAT vs. 5-HT transporter (SET) sites; (3) convenient preparation at high specific activity and radiochemical purity; (4) favorable radiation dosimetry and (5) striatal localization rate that is well matched to the physical $t_{1/2}$ of ^{99m}Tc .

15 The present invention has been described in detail, including the preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of the present disclosure, may make modifications and/or improvements of this invention and still be within the scope and spirit of this
20 invention as set forth in the following claims.